·S MELLITUS

on Children and
Adults

DIABETES MELLITUS

With Emphasis on Children and Young Adults

By

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Preface

It was my original thought to entitle this monograph "Diabetes Mellitus in Children" It soon became obvious that this entity could not be treated without presentation of the fundamental alterations in intermediary metabolism as they are now viewed nor without drawing comparisons and contrasts between the clinical manifestations and characteristics of diabetes in children and in adults Then too, it is amply established that survival of the juvenile diabetic is only part of the goal and that many of the problems which lie beyond the childhood and adolescence of the diabetic are common to all diabetics For these reasons it seemed far more descriptive to use the title 'Diabetes Mellitus, with Emphasis on Children and Young Adults"

T S D

Acknowledgments

In 1947 the Renziehausen Foundation, the Children's Hospital of Pittsburgh, and the University of Pittsburgh united in expanding the program of care of diabetic children, originally made possible by the generosity of Emelie Renziehausen, to include a research and service laboratory, a 17-bed hospital ward, outpatient clinics, and a professional staff Miss Renziehausen then set up Trust III which broadened the activities of this clinical and laboratory unit to permit studies in diabetes and in metabolic diseases in children and in adults This volume and the patient care, teaching, and research activities which made it possible are the direct products of the generosity of Miss Renziehausen To provide as broad an approach to the problem of diabetes as possible the physicians in the Renziehausen Program also assumed clinical responsibilities in the field of diabetes and metabolic diseases at the Presbyterian-Woman's, the Elizabeth Steel Magee and the Veterans Administration Hospitals as well as at the Falk Clinic which functions as the outpatient arm of the University of Pittsburgh Health Center At any one time these arrangements provide access to more than 1,000 patients with diabetes under the direct care of the Renziehausen unit and a large background of endocrine and metabolic problems in the Health Center and the affiliated institutions

It is obvious that an operation of this magnitude requires nurses, laboratory assistants, dietitians as well as social service, administrative, and auxiliary personnel too numerous to mention individually This is also true of the 46 physicians who in the course of nine years spent six months to two years as residents or Renziehausen Fellows providing the day-to-day care of the patients and participating in the program of clinical investigation and student instruction Were it not for their work this volume would be totally lacking in substance I must however name those who as colleagues past and present, have contributed so greatly to this program the late Lawrence Greenman, M D , F M Mateer, M D , F A Weigand, M D J H Peters, M D and R Tarail, M D

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Pittsburgh, Pennsylvania

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PART I

BIOCHEMICAL AND HORMONAL ASPECTS

CHAPTER 1

The Metabolism of Foodstuffs and the Defect in Diabetes Mellitus

The survival of any mammal involves the maintenance of body temperature within narrow limits transfer of nutrients for replacement repair or growth and release of secretions and other products of cell activity with subsequent transport to other tissues or to the external environment These processes all require energy Furthermore any somatic activity or the movement of the organism as a whole also requires energy to overcome inertia friction and gravity The energy for these processes is all obtained by enzymatic action from organic compounds in food and ultimately from the sun which provides the energy for their synthesis (1a–d)

In the past four or five decades the science of biochemistry has provided remarkable insight into the energy transformations that characterize living tissues Segments of this knowledge of the metabolism of the chief foodstuffs made available by the biochemist to the clinician and especially germane to an adequate understanding of diabetes mellitus will be briefly presented in this chapter Detailed reviews of metabolism and metabolic interrelationships are available elsewhere (1c–o)

I The Fate of Dietary Carbohydrate

A Digestion and Absorption

Enzymes for the hydrolysis of the complex carbohydrates in food such as starches and dextrins to simple sugars are present in the saliva in the gastric juice and in the secretions of the pancreas and the intestinal mucosa In the jejunum and ileum glucose fructose galactose and other dietary saccharides are absorbed by an active process possibly involving phosphorylation as well as by diffusion and enter the capillaries of the portal system (2a–d) It has been shown that the rate of absorption differs for each of the sugars and rises to a maximum of approximately one gram per kilogram of body weight per hour as an increased amount of a particular sugar is presented (2e f) This rate of absorption may be altered by several factors discussed in subsequent chapters of this text such as thyroid activity adrenocortical secretions and diseases such as sprue and

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The Metabolism of Foodstuffs and the Defect in Diabetes Mellitus

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celiac disease as well as by starvation, the fat content of the diet, and the presence of other sugars (2f)

B The Metabolic Fate of Glucose

Within the body fluids the chief dietary monosaccharide, glucose, may enter one of several metabolic pathways once it has crossed the cell membranes, or so-called "cytostructural interfaces" (3a) During this passage through the cell membrane, or shortly thereafter, glucose is phosphorylated i e, acquires a phosphate group through the mediation of the enzyme, hexokinase, and a high energy phosphate complex, adenosinetriphosphate or ATP (3b) The role, if any, of the anterior pituitary and adrenocortical steroids in this process of phosphorylation, remains controversial (3c–e) This phosphorylated derivative, glucose 6 phosphate, can then be converted to glucose 1-phosphate and glycogen, it may enter the glycolytic cycle for degradation to pyruvate or it may be catabolized to phosphoglyceraldehyde via the hexose monophosphate shunt The hexose mono-

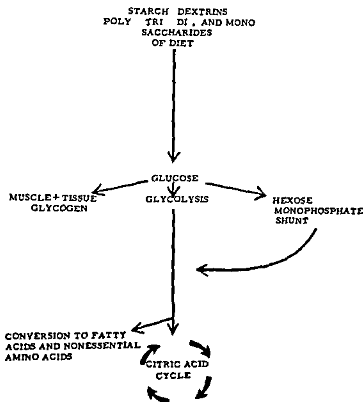


FIG 1 1 PATHWAYS OF GLUCOSE METABOLISM

phosphate shunt appears to be a major pathway of glucose catabolism in the liver These various possibilities are shown diagrammatically in figure 1-1 The retrograde reaction (glucose 6 phosphate → glucose + phosphate) may also occur but it does not of course represent a step in the degradation or disposal of glucose

1. Conversion to glycogen Glucose 6 phosphate derived from glucose or from other monosaccharides such as fructose or mannose, or from other sources such as lactic acid, amino acids or glycerol can be converted to glucose 1 phosphate and laid down in liver skeletal muscles, and other tissues as glycogen Glycogen is a polymer of glucose consisting of glucose molecules linked at carbon atoms one and four in the chain and one and six in the branches to provide a complex molecule with a molecular weight in excess of one million and perhaps in excess of four million (figure 1-2) (4a–f) The rate of storage of glucose as glycogen depends upon the store of liver glycogen and the availability of supplies of carbohydrate Glycogen storage is under the influence of insulin phosphorylase adrenocortical steroids glucagon epinephrine electrolytes and other variables It may

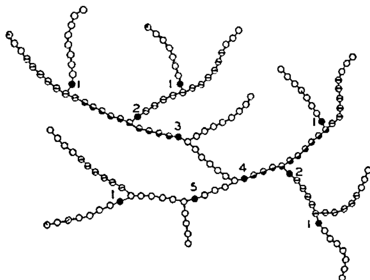


Fig 1 2 Branching of Glycogen Molecule

Model of segment of muscle glycogen based on results obtained by stepwise enzymatic degradation O ⊖, and ⊖ glucose residues removed by first second and third degradation with phosphorylase respectively ● glucose residues removed by amylo-1 6 glucosidase Of five tiers three were degraded corresponding to 122 out of 150 glucose residues (from Larner Illingworth Cori and Cori (4b) with kind permission of authors & publishers)

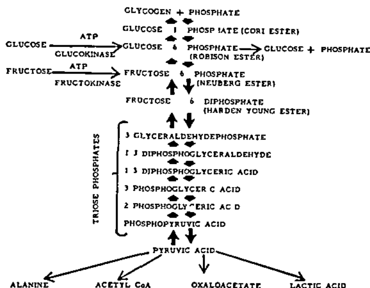
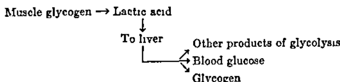


Fig 1-3 Glycolysis
Transformations are shown in accord with the schema of Embden Meyerhof Parnas (1i 5a) End products of pyruvic acid represent current views

be affected by disease states such as hyperthyroidism cirrhosis, and diabetes Supplies of blood glucose can be replenished from liver glycogen directly by glycogenolysis as follows

Liver glycogen → glucose 1 phosphate → glucose 6 phosphate
→ glucose + phosphate

The glycogen stores of muscle on the other hand cannot contribute directly to blood glucose because glucose 6 phosphatase is lacking in muscle Lactic acid *is therefore the end product of glycogenolysis However, once* the lactic acid leaves the muscle and enters the liver it can be converted to blood glucose or to liver glycogen (1c, 4g) This has been called the Cori cycle



2 **Degradation by glycolysis (anaerobic phase).** Many compounds have been identified as intermediates in the glycolytic scheme of Embden-Meyerhof-Parnas (1i, 5a, b) Some of these are listed in figure 1-3 Glycolysis may be described briefly as a process whereby glucose phosphorylated at the number six carbon is converted to fructose 6 phosphate,

phosphorylated in turn to fructose-1,6 diphosphate and then split into the first of a series of three carbon derivatives which are ultimately converted to pyruvate In this conversion of fructose-1,6-diphosphate to two molecules of pyruvate energy is generated and stored in the form of ATP

Since all the enzymatic reactions of the glycolytic scheme are freely reversible, pyruvate can go back through the glycolytic cycle all the way back to glycogen or, in the absence of oxygen, be converted to lactic acid It can be transformed to the amino acid alanine by the addition of an amino group (transamination) and to oxaloacetic acid by the addition of CO_2 Most important of all, it may be converted to acetyl CoA (1i, k, l, 5b) This last process is irreversible Acetyl CoA in turn may serve as a building block in the synthesis of amino acids, of fatty acids, ketone bodies and other products such as the steroids, or, and this is the major pathway, it can be oxidized to CO_2 and H_2O via the citric acid cycle of Krebs (6a, b)

3. Degradation via the hexose monophosphate shunt. The studies of Bloom, *et al* have indicated that in the liver some 75 per cent of the glucose-6-phosphate is degraded to phosphoglyceraldehyde after passing through phosphogluconate, ribulose, and ribose (7a–d) At this point the phosphoglyceraldehyde re enters the glycolytic cycle for subsequent transformation to pyruvic acid (figure 1-4) The quantitative significance of this shunt in the over all metabolism of carbohydrate *in vivo* is unknown *In vitro* studies indicate that this pathway represents only a small part of the total

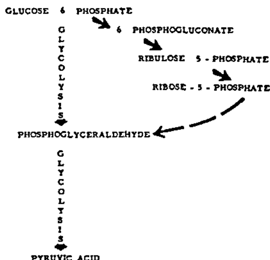


FIG 1-4 HEXOSE MONOPHOSPHATE (PHOSPHOGLUCONATE) SHUNT
The shunt is an alternative pathway for transformation of glucose-6 phosphate to phosphoglyceraldehyde (7c, d)

carbohydrate metabolism in striated muscle and in brain (7b) In bovine cornea it accounts for 35 per cent (7c)

4. Entry into the Krebs citric acid cycle (aerobic phase). Figure 1-5 depicts a simplified version of the Krebs cycle in which the chief intermediates are outlined This is the final common pathway for the degradation of carbohydrate, protein, and fat Acetyl CoA enters the Krebs cycle by condensing with oxaloacetic acid to produce a six carbon molecule, citric acid The conversions of citric acid to alphaketoglutaric acid and of the latter to succinic acid, each release a molecule of CO The net effect is the oxidation of acetyl CoA to CO_2 and H_2O and a generation of energy Most of this energy is stored in the form of high energy phosphate bonds (ATP) and thus is available to perform chemical work, i e synthesis of cell constituents, active transport, absorption, etc (6a, b)

II. The Intermediary Metabolism of Amino Acids and Proteins

A diet adequate in proteins, and adequacy will be quantitated later, provides certain essential amino acids as such or in the form of polypeptides in amounts sufficient for the construction or reconstruction of tissue

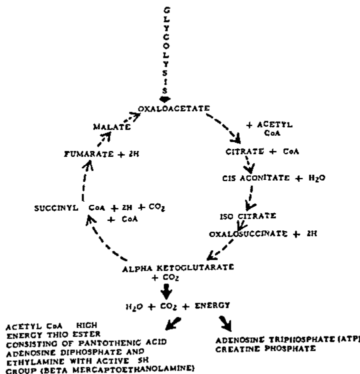


FIG 1-5 TRANSFORMATIONS WITHIN THE KREBS CYCLE (5b, 6b)

proteins Other nonessential amino acids can be synthesized from carbohydrate or other sources provided caloric intake is adequate Conversely amino acids taken in excess and not incorporated into proteins are deaminated in the liver and their carbon chains transformed into carbohydrate fat or even into other amino acids It has already been indicated in the preceding section of this chapter that carbohydrate thus formed can be deposited as glycogen or catabolized to CO and H_2O Also certain amino acids can enter the Krebs cycle through transamination the process whereby the amino group is transferred to an alpha ketoacid (6b) A readily available supply of energy as a result of the breakdown of acetyl CoA makes possible the *de novo* synthesis of proteins (1m)

A The Hydrolysis of Proteins in the Gastrointestinal Tract and the Assimilation of Polypeptides and Amino Acids

A number of gastrointestinal enzymes are capable of hydrolyzing the peptide linkages of proteins (—CONH—) with formation of amino acids and peptides These include the pepsin and renin present in gastric secretion and maximally effective in acid solution and the trypsin and chymotrypsin of the pancreas and the succus entericus which function most effectively in alkaline solutions There is now ample evidence that not all of the ingested protein must be split into amino acids prior to absorption (8a) The individual amino acids and polypeptides enter the portal circulation via an unidentified mechanism and reach the liver and thence the systemic circulation

B The Metabolic Fate of Amino Acids

1 **Incorporation into proteins** The turnover of proteins in tissues occurs at a half life rate of some 80 days and much more rapidly in plasma averaging 10 days in the case of albumin (8b) Appropriate amounts of all of the 20 or more amino acids are probably necessary for protein synthesis (8c) Transfer across the cell membrane and concentration within the cell is effected by an amino acid pump mechanism (8d) Protein is then synthesized largely and perhaps entirely within the microsomes of the cells (8e–j) (figure 1 6)

2 **Transformation or degradation in the liver, kidney, and in other sites** *a Transamination* is a biochemical process in which the amino group of an amino acid is transferred to an alpha ketoacid with formation of a new amino acid and an alpha ketoacid possessing the carbon chain of the initial amino acid Thus the transamination of alanine and alpha ketoglutarate results in the formation of pyruvate and glutamate This important reaction provides a link between carbohydrate and protein metabolism and represents a mechanism for the synthesis of amino acids from carbohydrate intermediates (8k)

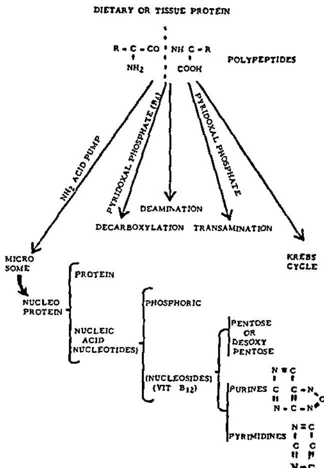


Fig 1-6 Metabolism of Proteins and Amino Acids

b Deamination and degradation In the liver, certain of the amino acids are converted to glucose following deamination (8l) The following amino acids have been shown to be glycogenic or gluconeogenic, i e giving rise to liver glycogen or in the phlorizinized animal to urine glucose glycine, serine, threonine, valine, glutamic acid, aspartic acid, proline, hydroxy proline, histidine, arginine, methionine, cystine, and tryptophan Leucine is the one amino acid that is solely ketogenic, i e productive of urine ketone bodies in the phlorizinized animal Glycogenic and ketogenic amino acids include alanine, isoleucine, phenylalanine, and tyrosine

The released amino group is in turn transformed into urea via the arginine citrulline ornithine cycle (8m) In the kidney glutamine becomes the source of ammonia and the ammonium ion so important in conserving certain body electrolytes as the need arises (8n)

C The Dietary Adequacy of Food Proteins The Concepts of Essential Amino Acids and of the Daily Protein Requirement

The studies of Rose and his collaborators have established that only certain of the amino acids present in body tissues can be synthesized from protein and nonprotein precursors The remainder have been called "essential", referring of course to the fact that they must be present preformed in the diet Obviously the human organism does not have the armamentarium for the biosynthesis of these compounds The group includes valine, leucine, isoleucine, methionine, threonine, tryptophane, lysine, and phenylalanine (9a–i) The remainder are termed nonessential since they can be synthesized and need not be obtained from exogenous protein sources

1. Amino acid mixtures versus whole proteins in maintenance of nitrogen equilibrium. This partitioning of the amino acids has been based largely upon the demonstration that the balance of body protein becomes negative, i e nitrogen loss is greater than intake, unless each of the essential amino acids is present in the diet in amounts above certain minimum values After many years of such studies it has become evident that whole unhydrolyzed proteins are more efficient in the maintenance of nitrogen balance than are the constituent amino acids obtained by hydrolysis (9j–l) This has given rise to the suggestions that either di- or polypeptides from partially digested protein are more effectively utilized or that the feeding of whole protein augments nitrogen retention This factor has been called the strepogenin effect The recognition of the existence of this effect will necessitate a revision of the estimates of the minimum dietary requirements of the individual essential amino acids

2. Attainment of nitrogen equilibrium following decreases in protein intake. Another relatively recent finding has further modified the views of the nutritionist concerning balances of body protein and nitrogen It has long been advocated that the adult diet should include one gram of "good protein", i e , one which contains essential amino acids in suitable ratios, per kilogram of body weight This recommendation arose in part from the observation that with lesser amounts the balance of body nitrogen becomes negative, i e , more is excreted in urine than is present in the diet This would be logical provided such losses were to continue unabated This is not the case however Thus, patients placed on regimens restricted in protein, such as the rice diet, ultimately again achieve nitrogen balance (intake = outgo) on a protein ration of 25 grams each day or approximately 0 3 gram per kilogram of body weight (10a–c) This is in keeping with the knowledge that much of the world survives on a protein intake of less than the American so called "optimum" At this point it behooves us therefore to recast our views and to establish the revised optimal intake value which will surely fall above the intake which produces liver disease

in the Bantu and which may well be below the accepted intake which leads to maximum growth It still remains to be established that maximum growth *per se* is an advantage Indeed it may ultimately be proved that similar to obesity maximum growth carries unnecessary handicaps with it

III Fats

Dietary lipids consist of neutral fats (esters of glycerol and fatty acids i e mono di , and triglycerides) free fatty acids sterols of animal and plant origin (the latter are not utilizable by the human organism but may influence the fate of cholesterol) complex fats such as the phospholipids lecithins cephalins and cerebrosides and finally waxes which are largely unassimilable Most and perhaps all of these are not essential components of the diet because in contrast to its limited ability to synthesize amino acids the body appears to be able to synthesize all or almost all of its fats from the other foodstuffs The proviso must be inserted in the light of the demonstration that linoleic linolenic and arachidonic acids must be included in the diet for the well being and grooming of the rat (11a) The general nonessentiality of the fats or lipids *per se* does not mean that they are not vital for the bodily economy but only that the organism is able to derive the vital lipids from other precursors Fats provide two and one quarter times the energy (nine calories per gram) obtainable from identical amounts of carbohydrate and protein The chemical nature and degree of unsaturation of ingested lipids modifies the type of lipid laid down as depot fat (11b) Finally we have just begun to recognize the deleterious effect of an unnecessarily high intake of calories from fat or the intake of excessive amounts of particular fats upon the incidence of cardiovascular diseases diabetes mellitus arthritis and gall bladder disease(11c d)

A Digestion and Absorption of Fats

Lipases or enzymes which break down glycerides into the component glycerol and fatty acids are present in the secretions of the stomach pancreas and small bowel but hydrolysis in the intestine need not be complete for absorption to occur(12a b) The glycerides fatty acids glycerol and cholesterol are then absorbed by the lacteals within the intestinal villi and enter the lymphatic drainage system of the trunk via the thoracic duct Fatty acids may enter the portal veins directly However the bulk of the assimilated fats by pass the liver upon absorption and reach this organ only after a partial circuit through the systemic circulation

B The Role of the Liver and Tissues in the Metabolism of Fats

Fatty acids ultimately reaching the liver from dietary sources or tissue depots are converted to acetyl CoA by successive oxidation at the beta

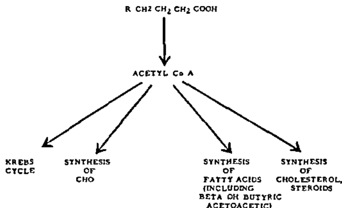


FIG 1 7 INTERMEDIATE METABOLISM AND FATE OF FATTY ACIDS

carbons in accordance with the original suggestion of Knoop (13a-c) (figure 1-7) Energy is liberated as the fatty acids are oxidized to CO_2 and H_2O (6b) This is mediated through transfers of protons and electrons to diphospho and triphosphopyridine nucleotides via transmitting enzymes (cytochromes) As already noted, in the untreated diabetic the citric acid cycle operates suboptimally As a result of reduced conversion of glucose to pyruvate oxaloacetate is not produced in adequate amounts from pyruvate for combination with acetyl CoA (see figure 1-5) The excesses of acetyl CoA are converted in part to acetoacetic and beta-hydroxybutyric acids and to acetone (figure 1-7)

Fat not utilized for energy purposes in the liver and other tissues is stored in depots The degree to which this occurs is determined by the metabolic load in relationship to the need and conditioning factors such as the adrenocortical and gonadal steroids The liver is also an important determinant of the form and amount of total circulating lipid (13d, e) Thus in obstructive disease of the biliary tract, total serum fat rises while in far-advanced cirrhosis it falls below levels present in health (13f) Under these circumstances also the proportion of circulating fatty acids in the esterified form is decreased below the rather stable value of some 70 per cent that obtains in subjects with intact liver structure and function (13g)

C The Concept of the Metabolic Pool

The dynamic state of body constituents and the interrelations of fat, protein and carbohydrate derivatives have been beautifully delineated in

Schoenheimer's Dunham Lectures (13h):

"The large and complex molecules and their component units, fatty acids, amino acids, and nucleic acids, are constantly involved in rapid chemical reactions Ester, *peptide, and other linkages open, the fragments thereby liberated merge with those* derived from other large molecules, and with those absorbed from the intestinal tract, to form a metabolic pool of components indistinguishable as to origin These liberated molecules are again subject to numerous processes Fatty acids are dehydrogenated hydrogenated, degraded or elongated, and thereby continually interconverted While *some individual molecules of these acids are completely degraded* other individuals of the same chemical species are steadily formed from entirely different substances notably from carbohydrate Similar reactions occur among the split products of the proteins The free amino acids are deaminated, and the nitrogen liberated is transferred to other previously deaminated molecules to form new amino acids Part of the pool of newly formed small molecules constantly re-enters vacant places in the large molecules to restore the fats the proteins and the nucleoproteins Some of the small molecules involved in these regeneration reactions constitute intermediate steps in the formation of excretory products

"Components of an animal are rapidly degraded into specific molecular groupings which may wander from one place to another The chemical reactions must be balanced so delicately that, through regeneration the body components remain constant in total amount and in structure This constancy is not to be taken as an indication that the structural matter of the living organism is inactive and takes little part in metabolism"

IV. Vitamins as Coenzymes in Intermediary Metabolism

The vitamins or accessory foodstuffs serve as coenzymes at many points in the intermediary metabolism of the chief foodstuffs

A Pantothenic Acid

Coenzyme A is a complex molecule consisting of pantothenic acid, adenosine diphosphate, and beta-mercaptoethanolamine (14a) The acetic acid ester of coenzyme A, acetyl coenzyme A, ranks with *adenosinetriphosphate* [illegible] able energy [illegible]

synthesis of fats, ketone *bodies and steroids Deficiency of pantothenic* acid decreases antibody production in rats, perhaps by decreasing protein synthesis (14d)

B Thiamine

This vitamin functions as a coenzyme (after hepatic conversion to the co-carboxylase, thiamine pyrophosphate) in the decarboxylation of pyruvate or other alpha ketoacids In the conversion of pyruvic acid to acetyl CoA, lipoic acid (6,8 dithiooctanoic acid) and thiamine are involved as coenzymes There is no conclusive evidence that lipoic acid must be provided in the diet

C Pyridoxine

Vitamin B_6 as pyridoxal phosphate is the essential coenzyme for all transamination reactions It also serves in the decarboxylation of amino acids (81) As in the case of pantothenic acid, a deficiency of pyridoxine decreases antibody production (14d)

D Choline

Choline in combination with phospholipids gives rise to lecithin (phosphatidyl choline) which facilitates in some unidentified manner the metabolism of fatty acids (14e, f) In the absence of adequate amounts of

from ethanolamine

E Folic Acid

This accessory food substance, N-5-formyl 5,6,7,8 tetrahydrofolic acid or folinic acid, is an important participant in reactions involving the transfer of one carbon fragments, as in the interconversion of glycine to serine (14h–j) and in the biosynthesis of the purine ring (14k) It also participates in antibody formation (14d)

F Vitamin B_{12}

Cobalamin (vitamin B_{12}) is operative in the synthesis of thymidine, a desoxyriboside, and possibly of desoxyribose itself (14l), in the formation of methyl groups, and in the interconversions of amino acids (14m) Its metabolic role remains obscure

V. The Action of Insulin and Possible Sites of Metabolic Defects in Diabetes

The work of Sanger has revealed that insulin is a protein with a molecular weight of 6,000, or multiples thereof (15) Each molecule consists of two polypeptide chains held together by —S—S— linkages derived from the amino acid cystine The A chain is made up of 21 amino acid residues and has glycine at its N-terminus, the B chain consists of 30 amino acid residues with phenylalanine as the N-terminal amino acid

There are several sites at which insulin, which escapes destruction by the insulinase or similar systems (16a–d, see also chapter 6), may act to facilitate the disposal of carbohydrate loads (16e)

A Effect of Insulin on Transfer of Glucose into Cells

Insulin may increase the rate of entry of glucose into the cells by altering the permeability of the cell membrane Levine and his colleagues (17a–c)

and others (17d–i) have demonstrated such an effect of insulin upon the volume of distribution of glucose, galactose, xylose, and arabinose and their uptake by the rat diaphragm Stadie (3a, 18) localizes this type of action at the "cytostructural" boundary of the cells Morgan *et al* (19) have concluded from studies of the kinetics of the transport of glucose and other monosaccharides that the process is not simple diffusion but an enzyme catalyzed or a "carrier" transport process, that it is symmetrical with respect to inward and outward movement, that it is not dependent on adenosinetriphosphate, and finally, that the rate at which such transport occurs sets the upper limits for glucose utilization

A CHAIN	B CHAIN
GLY	PHE
ISOLEU	VAL
VAL	ASP
GLU	GLU
GLU	HIS
CYS	LEU
CYS	CYS
ALA	GLY
SER	SER
VAL	HIS
CYS	LEU
SER	VAL
LEU	GLU
TYR	ALA
GLU	LEU
LEU	TYR
GLU	LEU
ASP	VAL
TYR	CYS
CYS	GLY
ASP	GLU
	ARG
	GLY
	PHE
	PHE
	TYR
	THR
	PRO
	LYS
	ALA

Fig 1-8 The Sequence of Amino Acids in the Insulin Molecule
In the 21 amino acid A chain glycine is present at the *N-terminus*. In the B chain of 30 amino acids phenylalanine makes up the N-terminus (15)

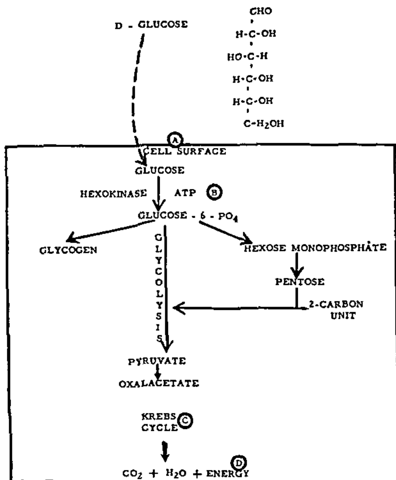


Fig 1-9 Possible Sites of Insulin Action

Insulin may facilitate the passage of the sugar through the cell membrane as at (A), facilitate phosphorylation of glucose (B), accelerate transformation within the Krebs cycle (C), or play a more specific role in the formation of high energy compounds (D) (3a) (Oxaloacetate is mispelled in the figure)

B Effect of Insulin on Phosphorylation of Glucose

Insulin may facilitate the phosphorylation of glucose within the cell, i e the formation of an ester of phosphorus, a process which requires an energy source such as adenosinetriphosphate and an enzyme The work of

Colowick and Cori and of others (3b, c, 20a, b) suggests that this is hexokinase The studies of Villee, White, and Hastings (20c) indicate that in the rat diaphragm insulin acts by cancelling the inhibitory action of growth and adrenocortical hormones upon hexokinase However, the difficulty encountered in demonstrating such a relationship in cell free systems (20d e) and in confirming the findings of Colowick (3e) raises appropriate doubts concerning the complete validity of this hypothesis This question remains unsettled since Hochstein *et al* (20f) have shown that glucose utilization can occur in special systems such as the cell free derivatives of mouse melanoma homogenates Once phosphorylation has taken place glycolysis proceeds down to pyruvate in the absence of insulin At this point, in the absence of insulin a block in the introduction of the products of glycolysis into the citric acid cycle by condensation with oxaloacetic acid appears (3e, 21a, b)

C Effect of Insulin on Transformations in the Citric Acid Cycle

The next site of possible insulin action is within the citric acid cycle itself as suggested by Krebs and Eggleston (22) Irrespective of whether it is the entry within the citric acid cycle or the transformations within it that are impeded by insulin lack, the net effect is defective production of adenosinetriphosphate with further interference with the phosphorylation which is mediated by high energy phosphate compounds In the presence of glucose, insulin favors the formation of esters of phosphorous at the expense of high energy phosphate compounds such as adenosinetriphosphate and creatine phosphate (23a)

In vitro studies with rat diaphragm provide some identification of variables which condition the action insulin As a first step in exerting its effect upon glucose uptake and glycogen synthesis insulin combines with the diaphragm (23b) Hypophysectomy or adrenalectomy has no discernible effect on the combination of insulin with the diaphragm, whereas pretreatment of the animals with anterior pituitary extracts or growth hor

of the alloxanized rat and the diaphragm *exposed in vitro to alloxan cannot* bind insulin The recent studies of Bornstein and Park (23e) indicate that hormonal factors may be operative in this defect because even serum from alloxanized diabetic rats also inhibits uptake provided that the pituitary and adrenal are intact

Recently Shaw and Stadie (23f) reported that in the rat diaphragm there are two pathways of glucose disposal a glycogen synthesizing pathway

which is insulin responsive and a lactate producing pathway which does not respond to insulin

Summary

The energy for growth, repair, and replacement of living tissues is derived from the complex organic molecules of foodstuffs and ultimately from the sun The carbohydrates, protein, and fats of the diet, absorbed following varying degrees of digestion, are ultimately but not entirely degraded to $CO_2 + H_2O$ (and N) with release of energy However, before this course is run, each of these foodstuffs or their derivatives may be incorporated into the structure and functions of the tissues at a rate which can be quantitated in terms of biologic half life Thus in the case of the carbohydrates the individual sugars may become components of the central nervous system cerebrosides, tissue glycoproteins nucleosides or be stored as polymers in the form of tissue glycogen The polypeptides and amino acids of proteins are used in the construction or reconstruction of body proteins The chief fate of uncatabolized fat is storage, though the individual lipids may be united with one of the other chief foodstuffs to form lipoproteins Also, components of carbohydrate, proteins and fats may be converted into the others Thus glucose can be transformed to nonessential amino acids or to fats, certain of the amino acids of protein may be deaminated and transformed to glucose or fatty acids, and the fatty acids can in turn be converted to amino acids and, perhaps only to a limited extent, to glucose

These interconversions of the major foodstuffs reflect of course the common pathways of catabolism of the foodstuffs Glycolysis, the chief route of glucose degradation, ends with acetyl CoA oxaloacetate, lactic acid, and alanine as the chief products The beta oxidation of fatty acids also results in the production of acetyl CoA which unites with oxaloacetate derived from glycolysis to enter the citric acid cycle The amino acids can enter the glycolytic cycle following conversion to glucose or, in the case of certain amino acid derivatives, may enter the citric acid cycle directly The end result is the degradation of complicated organic molecules with a release of energy for the formation of high energy esters of phosphorus (ATP and creatine phosphate) or of sulfur (coenzyme A)

In the diabetic the absence of insulin, or the increased destruction of insulin by insulinase or other systems greatly reduces glycolysis and decreases the availability of oxaloacetate Proteogenesis and lipogenesis are decreased The body shifts to fat for energy, but fatty acids are mobilized in excess of the catabolic capacities of the tissues Excesses of acetyl CoA

which accumulate are then converted to ketone bodies These two processes, together with increased *gluconeogenesis, account for the two chief* manifestations of diabetes, *i e*, hyperglycemia and excessive ketonemia It must be emphasized however that these characteristic findings in the absence of insulin result from changes in the *rates* of processes which normally occur in the body and do not represent the initiation of any new biochemical interconversions

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CHAPTER 2

The Morphologic and Metabolic Effects of the Growth-Diabetogenic and the Lactogenic Hormones of the Anterior Pituitary

The anterior pituitary elaborates a number of trophic or tropic hormones which have specific tissues as their targets and whose secretions in turn influence the utilization or disposal of foodstuffs In this chapter only the role of excesses and deficiencies of the diabetogenic-growth factor and of excesses of the lactogenic principle of the anterior pituitary will be discussed, with particular emphasis on carbohydrate metabolism The adrenocorticotropin-adrenocortical, the thyrotropin-thyroidal, and the gonadotropin gonadal effects will be presented in outline form only in clarifying the role of the anterior pituitary, and then taken up separately and in detail in the succeeding chapters In Chapter 6 the possible bearing of variations in these hormones, contrived in nature and by man, upon the clinical entity known as diabetes mellitus will be evaluated

I. Effects of Losses of Growth and Other Pituitary Hormones

A In Nondiabetic Animals

The removal of the anterior hypophysis produces a cessation of growth in the immature animal, in the adult a decreased food intake, weight loss, hypoglycemia, and cachexia supervene (1a–f) Since this procedure deprives the organism of all of the anterior pituitary tropic hormones, such animals exhibit morphologic changes in the target glands consisting of a decrease in the organ and cell size, and evidence of diminished secretory activity in the thyroid (1g), in most but not all of the cells of the adrenal cortex (1h), and in the gonads (1i) From the viewpoint of function the changes consist of a) hypothyroidism (decreased iodide and iodine trapping, diminished formation, storage, and release of thyroxin, and decreased oxygen consumption), b) hypoadrenocorticism 1) water and electrolyte regulation variable limitations in the facilitation of potassium and water output and in the conservation of sodium during periods of deprivation, redistribution of water and electrolytes within the body, 2) regulation of the intermediary metabolism of foodstuffs, a tendency to hypoglycemia as a result of an increase in glucose tolerance and an increase in sensitivity

to insulin arising in part from diminished gluconeogenesis from protein and fat and decreased glycogen formation and storage, 3) *integrity of* secondary sex manifestations androgenic, *i e*, the protein-anabol[illegible]

[illegible] and sperm and decrease or loss of sexual characteristics and activities (1j, k))

Anterior pituitary extracts which contain sufficient amounts of the tropic principles correct all of these deficiencies in growth as well as the morphology and function of the adrenal cortex, thyroid, and gonads Extracts rich in growth hormone correct the deficiencies in growth and overcome in great measure the alterations in carbohydrate metabolism Cancellation of the thyroidal, the adrenocortical, and the gonadal deficiencies in such animals requires the specific tropic hormone, though in the case of the thyroid, the adrenal cortex, and the nongametocyte function of the gonads animals or synthetic derivatives can serve as replacements for the products of these glands

B In Diabetic Animals

Houssay *et al* (1b, 2a, b) demonstrated that the removal of the anterior hypophysis markedly alleviated the manifestations of the diabetes which followed complete pancreatectomy in animals The hyperglycemia and glycosuria recurred with administration of anterior pituitary extracts Though Long and Lukens (3) showed that adrenalectomy produced a similar amelioration of the diabetic state following pancreatectomy, the fact that combined anterior hypophysectomy-adrenalectomy produced a greater effect than either alone suggested that the mechanisms involved might not be identical The validity of this conclusion has been established in subsequent studies with purified derivatives of the anterior pituitary and of the adrenal cortex and in the case of the latter, with synthetic steroids as well

II. Effects of Anterior Pituitary Extracts: Older Experimental Work

The injection of crude extracts of the anterior pituitary overcomes, in part at least the cessation of growth and the tendency to hypoglycemia which characterizes the animal deprived of the anterior hypophysis and produces excessive growth and hyperglycemia in the intact animal

The growth effects when obtained, consist of an increase in body size and in the muscles viscera, and the features of animals (4a, b) resembling those seen in the giantism and acromegaly in patients with eosinophil adenomata of the anterior pituitary In pregnant rats an increase in body size has been noted in the mothers and offspring (5)

The hyperglycemia which appears with the administration of growth hormone to susceptible species and individuals is accompanied by glycosuria and ketonemia (6a g) and resembles therefore diabetes mellitus which appears spontaneously in humans In some of the animals the carbohydrate disorder persists after the cessation of therapy and is termed metahypophyseal diabetes

Houssay (6h) reported that morphologic changes in the beta cells of the pancreatic islets (degranulation hyalinization and in the animals with permanent diabetes atrophy or disappearance of islets) were found in animals receiving such anterior pituitary extracts Lukens and his colleagues (7a b) subsequently showed that in partially depancreatized rats cessation of pituitary extract therapy or treatment with insulin or with phlorizin prior to the end of the third month permitted recovery of the islets and avoided a permanent diabetes

III Effects of Anterior Pituitary Derivatives Studies with Purified Growth Hormones

A Is Growth Diabetogenic Hormone a Single Entity?

The purification procedures devised by Li Evans and Simpson (8a) and by Wilhelmi Fishman and Russell (8b) applied to homogenates of pituitaries have yielded growth hormone a protein which is capable of inducing a resumption of growth following hypophysectomy and which produces hyperglycemia glycosuria and ketosis in suitable animals This material is free of significant amounts of other pituitary proteins such as thyrotropin adrenocorticotropin and gonadotropins Since crystallization electrophoresis and x ray diffraction patterns indicate this to be essentially a pure protein it has been generally agreed until recently that it represents a single molecule capable of exerting these dual actions In 1951 Raben and Westermeyer (8c) reported that a growth hormone obtained from hog pituitaries by passage through an oxycellulose column had no effect upon carbohydrate metabolism but retained its ability to restore growth following anterior hypophysectomy This could be taken to indicate that despite the seeming uniformity of pure growth diabetogenic hormone preparations two very similar but distinct proteins are present Chromatographic separation on an oxycellulose column merely utilizes these slight differences to effect a separation These studies have also yielded a diabetogenic protein material which is associated with corticotropin rather than with growth hormone in the chromatographic separation and which may be an entity distinct from these two known pituitary tropic factors (8d e) If the anterior pituitary does elaborate this diabetogenic factor as a separate hormone then the long recognized carbohydrate effects of crude anterior pituitary extracts such as the ability to produce

hyperglycemia, ketosis, and insulin resistance, to mobilize fat, and to lower the RQ (6a) will have to be ascribed to it rather than to growth hormone However, a number of workers (9a, b, c) have been unable to confirm the findings of Raben and Westermeyer It is still possible therefore that growth-diabetogenic factor is a single entity as Young (9d, e) and Reid (9f) and others have emphasized and that these newer separation procedures merely alter the growth-diabetogenic hormone molecule sufficiently to remove its diabetogenic properties The effect of a variable such as pH on the ionization of protein is in keeping with this possibility, and there is some evidence that in alkaline media growth-diabetogenic hormone loses some of its carbohydrate effect (9g, h)

These unsettled questions are to be kept in mind in the presentation of the morphologic and metabolic effects of the so-called growth-diabetogenic factor which follows

B The Morphologic Effects of the So-called "Pure" Growth Hormone

The earlier observations that crude or relatively impure preparations of pituitary growth factor produced body growth in hypophysectomized and normal animals (4a), increased muscle size (4b), and induced degranulation, "hyalinization", and atrophy or disappearance of the pancreatic beta cells (6h) have been confirmed with highly purified growth hormone obtained by separations of the type described by Li (8a) and Wilhelmi (8b) and their colleagues

Thus the newer derivatives are much more potent in producing body weight gain in the immature hypophysectomized mouse (10a, b), but may be inactive in the monkey (10c) Bigland (11a), Greenbaum (11b), Simpson (11c) and their co-workers have specifically commented on the increases in muscle size The individual fibers of skeletal, cardiac, and connective tissues have also been reported to be increased in diameter The effect on the individual muscles may be proportionate to or in excess of the gain in body mass In Bigland s animals the tension exerted by the enlarged quadriceps was found to be less than in normals (11a)

It has been shown that purified growth hormone increases skeleton size but not maturation (12a) and that the thyroid gland plays a determinative role in the latter The increase in the width of the epiphysis induced by growth hormone is quantitatively related to dosage and is the basis for a bioassay, provided suitable allowances are made for the effects of lactogenic hormone and the less marked action of thyrotropin and adrenocorticotropin (12b–d)

Similarly, the newer preparations continue to produce the changes in pancreatic islets described with the crude materials (6h, 13a) Haist and Kinash (13b) have in addition reported an actual increase in islet weight,

but the injected hypophysectomized animals ate more than the hypophysectomized controls

C Biochemical Changes Induced by Growth Hormone

1. In the Metabolism of Protein and Nitrogen. The increases in body weight, organ and cell size and the accelerated skeletal growth are reflected of course in the external exchanges of nitrogen, as well as in the relative rates of anabolic and catabolic processes within the body Effective preparations of growth hormone decrease the urinary excretion of nitrogen (14a, b) and increase the protein content of muscle, of circulating plasma, and of other organs and tissues (14c–g) This positive nitrogen balance could result from decreased protein breakdown, diminished degradation of released amino acids, or increased synthesis of amino acids into body proteins The studies of Bartlett, using glycine tagged with N^{15}, suggest that all of these factors are operative as indicated by decreased protein degradation in the fasting dog given growth hormone (15a), a lower rate of amino acid catabolism, a smaller urea pool, a larger pool of metabolic nitrogen, and an accelerated rate of incorporation of tagged glycine into protein (15b) Russell (15c) on the other hand believes that, in the presence of an adequate supply of amino acids and with the organism operating largely upon a fat substrate, the chief and perhaps the sole effect of growth hormone is exerted on protein anabolism She points out that in Hoberman's studies (15d) the total nitrogen excretion in fasting animals was reduced by growth hormone with a proportionate decrease in the excretion of previously administered tagged nitrogen This argues against an inhibition of protein catabolism since under such circumstances the decrease would not have been proportionate The drop in plasma and tissue amino acids (15e, f) and the accelerated disposal of exogenous amino acids following growth hormone (15g) argue against a depressant effect upon amino acid catabolism It may well be that the isotope studies detect rate changes which in terms of net effect prove insignificant The detailed evidence for these two interpretations is available in several reviews (15h–j)

It should be pointed out that the nitrogen retaining effect of growth hormone cannot be elicited in a pancreatectomized preparation, as for example, in a Houssay animal (16a) Insulin therefore is necessary for the growth effects of growth hormone Furthermore, insulin itself can serve as a growth hormone in a hypophysectomized animal though it is not effective to the same degree (16b, c) This has suggested the interesting possibility that a major portion of the growth stimulating effect of anterior pituitary principles is mediated through an increased insulin output (16a, d)

2. In Fat Metabolism. It has been shown that growth hormone administration mobilizes lipid from tissues and deposits it in the liver (17a, b) Also, in terms of the intermediate metabolism of fat it has been recognized since the days of crude pituitary extracts that growth factor is ketogenic Studies with liver slices show that the hypophysectomized rat produces fewer ketone bodies (17c, d) and that growth hormone inhibits lipogenesis (17e) It is not entirely clear that these are direct effects on lipid metabolism, since inhibition of carbohydrate metabolism, an action of growth hormone, is by itself ketogenic (16a) Moreover, Petersen and Lotspeich have suggested that the ketogenic effect is not obtainable with purified growth hormone (17f) Engel after reviewing possible sites of metabolic blockade concluded that growth hormone probably acts at some undetermined point in the Krebs cycle (8e) Russell's thesis (15c) that a fat substrate is conducive to the protein anabolic action of growth hormone has already been cited This view is supported by the studies of Bondy (17g) and of Beaton and Curry (17h)

3. In Carbohydrate Metabolism. Until the advent of the Raben-Westermeyer preparation all active forms of the growth hormone exerted a deleterious effect on carbohydrate disposal which paralleled the growth activity (9c–f)

a *Initial hypoglycemia or hyperglycemia?* The earlier finding that the materials first produced degranulation of the beta cells (6h) led to the suggestion that they increased insulin secretion (18a c) The finding by Milman (15e) and Kurtz (19a) and their colleagues that hypoglycemia appeared shortly following the initial injection of the newer derivatives is in keeping with such an action, though it should be noted that in the work reported by Kurtz pancreatectomy failed to eliminate this acute hypoglycemia Furthermore the studies of Foà (19b), of Bornstein (19c) and of Kibler (19d) and their colleagues indicate that transient early [illegible] ggested that this [illegible] is elimi [illegible] owever, [illegible] ment is [illegible] purified growth hormone Perhaps some of the answers lie, as has been suggested, (19e) in the level of blood sugar at the time of injection

b *Subsequent hyperglycemia and diabetes* In contrast to the uncertainty concerning the earliest effects, it is clear that several days of growth hormone therapy at a level of approximately three milligrams per kilo gram of body weight produced hyperglycemia, glycosuria, ketosis and weight loss in susceptible species and individuals This experimental form of diabetes is characterized by impaired glucose tolerance (20a, b) which

responds to insulin therapy (21a, b 22) The diabetogenic effects can be elicited in the pancreatectomized (6d), in the alloxanized (23a, b), and in the adrenalectomized preparation (24) In the intact animal the pancreatic islets show the lesions described following crude extracts, with evidence of increased activity and new islet formation However, continued therapy results in destruction of the islets and permanent diabetes Perfusion of the pancreas of such animals shows a diminished insulin output (25), histologic measurements point to loss of islet tissue, and extractions reveal a decreased insulin content It has already been mentioned that not all species nor members of a particular species respond to this diabetogenic effect The studies of Adams and de Bodo (26a) and of Emerson (26b) indicate that a tolerance or unresponsiveness to this action of growth hormone develops in susceptible animals which can be overcome by increasing the dosage or shifting to growth hormone derived from another species

c Site of diabetogenic action The exact point in the metabolism of glucose at which the diabetogenic effect of growth hormone is exerted (*i e*, at the entry of glucose into cells, glycolysis, the hexose monophosphate shunt, citric acid cycle or in the regeneration of high energy phosphate) has not been established Studies of I^{131} labelled insulin indicate that destruction of insulin is not accelerated in homogenates which contain anterior pituitary derivatives, though it is retarded by anterior hypophysectomy This suggests that a relative deficiency of insulin due to destruction is not a contributing factor (27a, b) Also one may conclude from the volume of distribution studies of Levine *et al* that penetration of glucose into cells is not retarded (see section V of Chapter 1)

4. In Electrolyte and Water Metabolism. Therapy of animals with growth hormone which is effective in producing body weight gain and increase in body tissues should be accompanied by decreased urinary output and retention of the chief extracellular and cellular electrolytes The reports of Glafkides (14a) Stein (14c), and Whitney (14f) and their colleagues demonstrate positive balances of sodium, potassium, and chloride as a result of growth hormone administration but no data on phosphorus are given The lack of an effect of growth hormone on this constituent reported by Knobil (10c) was observed in monkeys which did not respond to therapy It is probable however that growth hormone does alter phosphorus metabolism especially since it is recognized that in humans the level of serum inorganic phosphorus is elevated during active acromegaly and decreases with successful therapy of the eosinophil adenoma (27c, d)

The data on net body fluid effects of growth hormone are scant It has been shown that the inability of the hypophysectomized dog to excrete a water load is partly corrected by growth hormone (28a) In the intact animal such therapy results in an expansion of extracellular and cell water

as measured by the thiocyanate space or by analyses of muscles (14f, 28b) Studies of plasma show that a decrease in hematocrit is produced which, from measurements of the total red cell volume and circulating plasma proteins, represents an expansion of plasma volume (28c)

IV. Effects of Anterior Pituitary Growth Hormone Therapy in Humans

With but a few possible exceptions growth hormone administration to healthy adults and to dwarfs has had no clinical effect upon body growth, *and has only rarely influenced the* balances of nitrogen and electrolytes (12a, 29a–j) Studies in our laboratory on muscular dystrophy children undergoing a therapeutic trial of growth hormone prepared in accordance with the Raben-Westermeyer technique showed no change in body growth, in nitrogen and electrolyte balances, nor in carbohydrate metabolism as reflected in responses to oral or intravenous glucose or to intravenous insulin (29k)

V. Clinical Hyper- and Hypofunction of the Anterior Pituitary

In patients with loss of anterior pituitary function, such as those with Simmonds' disease or Sheehan's syndrome, hypoglycemia may be pres*ent and hypersensitivity to insulin can be demonstrated (30a–d) This is* in keeping with the effects of ablation of the anterior pituitary in animals

Adenomata of the eosinophil cells of the anterior pituitary produce giantism during the growth period and acromegaly and splanchnomegaly thereafter This increased secretion of growth hormone by the eosinophils of the anterior pituitary is associated with a higher incidence of diabetes

ability to produce insulin are greater in the nonsusceptibles or that the expanding eosinophil adenomata produce deficits of adrenocorticotropin, *thyrotropin, and other factors* which influence carbohydrate metabolism It must also be kept in mind that such patients may eat poorly

VI. The Diabetogenic Effect of Prolactin

Changes in carbohydrate metabolism *have been noted to follow the in*jection of another pituitary tropic hormone, prolactin This was perhaps first noted by Houssay and Anderson (2b) but their lactogenic preparation contained up to 30 per cent ACTH Fox and his co-workers have shown that the administration of a purer form of lactogenic principle isolated from animal pituitaries to intact dogs produces initial hypoglycemia which is then followed by hyperglycemia (32a–e) Pancreatectomy eliminates

the hypoglycemic but not the hyperglycemic phase This suggests that the lowering of the blood sugar is produced by release of pancreatic insulin and eliminates the possibility that the subsequent hyperglycemia is attributable to a release of glucagon or hyperglycemic glycogenolytic factor which may be secreted by the alpha cells (see Chapter 11) Examination of the pancreas of animals following the first intravenous injection of prolactin reveals degranulation of beta cells suggestive of insulin release (32a–c) The etiology of the subsequent hyperglycemia remains obscure but it may be related to the diabetogenic effect of estrogens released in small amounts by the gonads in response to prolactin This possibility and the findings that estrogens in large dosage may ameliorate diabetes are discussed in Chapter 4

Summary

Chromatographic separation of anterior pituitary extracts has resulted in the preparation of a growth factor which is free of diabetogenic activity This suggests that perhaps growth and diabetogenic properties of anterior pituitary extracts reside in two separate though closely related molecules This remains however a controversial issue

The administration of extracts of the anterior pituitary or of apparently pure growth diabetogenic hormone produces in several days hyperglycemia glycosuria and ketonuria in susceptible individuals of susceptible animal species The finding of an initial hypoglycemia and the histologic study of the pancreas have led to the suggestion that the growth diabetogenic factor stimulates the beta cells directly and ultimate destruction of these insulin producing cells results from a combination of stimulation and exhaustion Evidence is also available indicating that pancreatic glucagon is released by growth hormone

The diabetogenic effect appears to rise entirely from a blockade of insulin action at the cell level (in the rat diaphragm conversion of glucose to glycogen is impeded) without evidence of increased gluconeogenesis As a matter of fact growth diabetogenic hormone facilitates the incorporation of amino acids (and other tissue constituents) into tissue proteins and thereby removes a potential source of glucose

Prolactin or the lactogenic hormone of the anterior pituitary apparently free of the growth diabetogenic factor is also capable of producing diabetes Again there is evidence that this hormone like the growth diabetogenic factor initially stimulates a release of insulin by the beta cells

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CHAPTER 3

Products of the Adrenal and the Metabolism of Carbohydrate

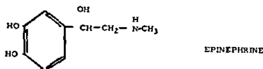
Though it is well known that changes in carbohydrate metabolism are produced by derivatives obtained from the medulla and cortex of animal adrenals as well as by synthetic congeners the mechanisms of these actions and the sites at which they occur are not as yet clearly defined Comparable alterations in carbohydrate metabolism may also be encountered in the course of spontaneous increases in the activity of these organs, as in pheochromocytoma or adrenocortical hyperplasia while opposite effects are at times seen with deficiencies of certain of the humoral products of the adrenals

I The Adrenal Medulla

A The Role of Hyperglycemia of Medullary Origin

Extracts of this portion of the adrenal have long been known to produce hyperglycemia (1) Cannon (2a–c) in his writings assigned a useful role to this hyperglycemia in the primitive reaction to alarm which prepared the organism for combat or for flight This may have been true in the evolutionary history of the progenitors of man, but in the highly organized biochemical economy of mammals as they exist today its possible effectiveness as a ready mobilizer of energy is largely lost as a consequence of though not necessarily directly mediated by (3a–e), a concomitant discharge of adrenocortical steroids These agents, discussed in section II of this chapter, act to cancel the increased utilization of carbohydrate to be expected from hyperglycemia *per se* Hence, if such an explanation of hyperglycemia originating from products of the adrenal medulla is used, it is necessary to indicate that it may represent an attempt to overcome the block in carbohydrate metabolism imposed by the secretions of the cortex of this gland

It had been suspected from pharmacologic studies that there may be two different effects or components in the total extract known as epinephrine or, more commonly, adrenalin (4) In 1949 the two pressor amines, epinephrine and norepinephrine, present in extracts of the medulla were characterized chemically (5a–c) Their chemical structures are shown



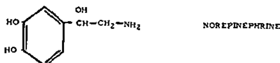


FIG 3-1 CHEMICAL STRUCTURE OF EPINEPHRINE AND OF NOREPINEPHRINE

in figure 3-1 and some of their known physiologic actions other than the hyperglycemic effect are compared in table 3-I (6a–l)

B The Origin of Medullary Hyperglycemia

The subcutaneous administration of the whole extract of the medulla, or of either of its two components produces a prompt rise in the level of the blood sugar The degree of this response and its duration in healthy subjects is shown in figure 12-1 of Chapter 12 It originates largely as a consequence of activation of liver phosphorylase with depolymerization of liver glycogen (7a–e) Conversion of muscle and perhaps other tissue glycogen to glucose (via the pathway muscle glycogen → lactic acid ⇄ glucose 6 phosphate → blood sugar or liver glycogen) (8a–h), gluconeogenesis from at least fat (9a–d), and decreased peripheral utilization (10a–d) also play contributary roles However, the last point has been disputed (10e–g) (see Chapter 12)

1. Findings in Muscular Dystrophy. Studies with muscular dystrophy in our laboratory (11a, b) confirm the earlier observations of Elkington and Goldblatt (11c) in showing a distinctly lower hyperglycemic response to epinephrine This we have taken to indicate a decreased availability of muscle glycogen *in this disease entity for ultimate conversion to blood* sugar

It is possible however that this difference is to be ascribed to defects in liver phosphorylase, undue tenacity of liver glycogen, diminished epinephrine blockade of peripheral glucose utilization, decreased stores of hepatic glycogen, or to liver disease (11b) There is no evidence for at least the last two of these possibilities (11d, e) and it has been established that the

TABLE 3 I

Comparison of physiologic effects of epinephrine and norepinephrine

Measurement	Reference	Epinephrine	Norepinephrine
Cardiac output	6a b h	Increased	No change decreased
Systolic blood pressure	6a b h	Increased	Increased
Diastolic blood pressure	6a b h	No change	Increased
Pulse rate	6a b	Increased	Decreased
Peripheral resistance	6a b	Decreased	Increased
Glomerular filtration rate	6c d	—	No change
Clearance of Na	6c d j k l	Increased decreased	No change decreased increased
Clearance of K	6c d j k l	Decreased	Decreased no change
Portal pressure	6i	Increased	Increased +

responses in cirrhosis to epinephrine though abnormal, are of a different type (12) On the other hand it has been shown that muscle glycogen stores are abnormal in experimental muscular dystrophy (11d) and that glycogenolytic enzymes are altered in patients with this disease (13a)

2 Responses in Juvenile Diabetes The young diabetic responds with hyperglycemia to the whole extract of the adrenal medulla to norepinephrine and to epinephrine (see figure 12 3 in Chapter 12) The quantitatively greater change in terms of prolongation of the hyperglycemia is compatible with a relative inability of the diabetic without insulin to dispose of the carbohydrate load thereby presented (13b) This is al o evident in the concomitant electrolyte changes in these two groups of subjects as described in detail in Chapter 12

C Electrolyte Changes Accompanying Hyperglycemia of Medullary Origin

As indicated in Chapter 1 the disposal of glucose loads may occur through at least three pathways glycogenation glycolysis and the hexose monophosphate shunt which rejoins glycolysis at the point at which *phosphoglyceraldehyde is formed* In view of the deglycogenating action of epinephrine it is obvious that at least at the height of the epinephrine action only the latter two pathways are available Nothing is known about electrolyte cl anges during the operation of the hexose monophosphate shunt but glycolysis is accompanied of course, by phosphorylation This abstracts inorganic phosphorus from the serum In the juvenile diabetic the decrease in concentration of serum inorganic phosphorus follow

ing epinephrine is less than in the nondiabetic control despite the more prolonged rise in blood sugar in the diabetic patients These and the changes in the other electrolytes are described in greater detail in Chapter 12

D Pheochromocytoma Clinical Hyperadrenalism of Medullary Origin

The earlier clinical reports of pheochromocytoma emphasized the occurrence of episodic hyperglycemia or glycosuria as diagnostic features (14a–f) Glucose tolerance tests were also abnormal at times All of these changes are in keeping with the known hyperglycemic effects of epinephrine and the loss of tolerance for glucose which accompanies deglycogenation of the liver and the epinephrine-induced peripheral blockade of glucose disposal (15), if such there be

However, as knowledge of this syndrome has increased through autopsy material consisting of previously undiagnosed pheochromocytomata, it is evident that carbohydrate changes are not indispensable features As a matter of fact, hypertension intermittent or persistent, may be the sole finding (14d) Hence carbohydrate alterations, like the responses to the histamine, adrenolytic, or cold pressor tests and the signs of autonomic overactivity such as sweating, tachycardia, or increased basal metabolic rate, may or may not be present in this entity

E Carbohydrate Effects of Demedullation

Though loss of the adrenal medullae leads to insulin hypersensitivity (16a–c), there is no evidence of any associated spontaneous carbohydrate disturbance There are no data concerning hyperglycemic and electrolyte changes following adrenalin administration to such subjects or patients, though they may well occur

II. The Adrenal Cortex

All three of the major groups of steroids isolated from the adrenal cortex (the 11-desoxy, 11-oxy, and androgenic) have been shown to affect the intermediate metabolism of foodstuffs in addition to any other mineral-regulating and androgenic actions which they may possess

A Carbohydrate Effects of an 11-Desoxysteroid, DOC

11-Desoxycorticosterone or DOC has relatively little capacity to induce glycogen deposition in the liver of adrenalectomized animals when com-

pared to the 11-oxysteroids such as cortisone or hydrocortisone by means of bioassay (17a–j) The low rating is in keeping with the clinical experience that in Addison's disease DOC does not provide adequate control of hypoglycemia (18a) The appearance of a more normal oral glucose tolerance curve in Addison's disease following DOC in place of the flattened response seen in the untreated patient is largely, and perhaps entirely, attributable to the restoration of circulatory efficiency as sodium and water deficits are corrected by the predominant mineral-regulating action of this hormone Cortisone does not have this action in adrenalectomized rats (18b) DOC itself in subjects with functioning adrenal cortices may ameliorate clinical and experimental diabetes (19a–c) The fact that adrenalectomy does the same suggests that both procedures remove a diabetogenic factor (19d–f)

Until the advent of aldosterone or electrocortin isolated by Reichstein *et al* (20a–c) in 1953, a mineral regulating steroid some 25 times more potent than DOC, it had been convenient and justifiable to believe that the absence of oxygen from the 11-position strengthened the mineral-regulating effect of a steroid and weakened its carbohydrate effects DOC and cortisone were usually contrasted in this regard, since the latter possesses but 1/25 of the electrolyte effects of DOC, milligram for milligram, while it exerts a far more potent influence on the intermediary metabolism of foodstuffs The demonstration that aldosterone is an hemiacetal with an oxygen in the 11-position has upset this neat classification This steroid, present in the amorphous fraction of extracts of the adrenal cortex of animals and isolated from the urine of patients with disorders of mineral regulation, as in nephrosis and adrenocortical hyperactivity or tumor (20d–g), exerts a mineral regulating effect more marked than that exhibited by DOC It also possesses a capacity to induce glycogen deposition which, in comparable amounts, is almost as great as that of cortisone or hydrocortisone (20g) However, since aldosterone is secreted in much smaller amounts than is true of hydrocortisone it is improbable that the endogenous output does significantly influence carbohydrate metabolism Its chief role appears to lie in the regulation of sodium, potassium, and water excretion in conjunction with other steroids of the adrenal cortex In the normal animal it facilitates the reabsorption of sodium from the distal tubule and enhances the renal excretion of potassium This is also true in the adrenalectomized water-loaded animal in contrast to the sodium diuretic effect exerted by steroids such as hydrocortisone (20h)

Presumably the alterations in chloride excretion induced by aldosterone are secondary to the sodium change This is certainly true in the case of DOC (21), though it has not been demonstrated for aldosterone

B The Effects of 11-Oxysteroids Upon the Metabolism of Foodstuffs and of Carbohydrate in Particular

Steroids of this type, such as Cpd E or cortisone (17α hydroxy 11-dehydrocorticosterone), Cpd F or hydrocortisone (17α-hydroxycorticosterone), Cpd B (corticosterone), or Cpd L (allopregnan 3β,17α,diol 20 one) produce distinct metabolic changes when administered to normal subjects in pharmacologic dosage, i e, 50 mg or more each day The first of these steroids is present only in small amounts in venous blood obtained from humans or from the catheterized adrenals of animals (22a, b) and hence is looked upon as largely a laboratory product The others are among the 30-odd steroids which have been isolated from the adrenals (22c–e)

1. Effects on Protein The administration of any one of the compounds cited, or of ACTH, to healthy subjects produces an antianabolic effect, i e, *the ordinary day-to day replacement of tissue proteins is decreased while* breakdown continues at an unabated or increased rate (23a–c) The work with N^{15}-tagged glycine and related technics shows that the incorporation of administered amino acids into body protein is retarded by adreno cortical steroids (24a–f) A negative balance of nitrogen or interference with protein synthesis results In the earlier studies a rising uric acid creatinine ratio in urine was employed as an index of this effect, but this has been abandoned largely because it is erratic and cumbersome (25)

This net catabolic effect of administered 11-oxysteroids has been frequently observed in animals, in healthy human subjects, and in patients (26a–l) However, in many patients this negative balance of nitrogen may not be present, or, if present, soon disappears in the face of continued steroid therapy (26i–l) Our experiences in this regard have been summarized elsewhere (26m) The reappearance of nitrogen equilibrium or the development of actual nitrogen retention represents a beneficial effect of 11 oxysteroids which cancels the so called ' toxic destruction ' of protein in illness (27a b), if such there be, and leads to nitrogen storage in excess of the expected antianabolic effect of the hormone It becomes evident only when a high caloric high-nitrogen intake is provided and especially at a time when the patient is beginning to improve The studies of Rupp, Paschkis, and Cantarow (28a) indicate that the administration of potassium salts has no nitrogen sparing effect under circumstances which lead to negative balances of body protein during steroid therapy, but these results differ from the earlier findings of Whitney and Bennett (28b, c) Measurements of amino acids following adrenocortical oxysteroids show a rise to be present regularly in the plasma, though the effects upon individual amino acids are variable (29a f) and the changes in tissues vary with the organs studied (29g) Thus the kidney is but little affected, the liver shows a general though not universal decrease, and the amino

acids, with some exceptions, increase markedly in the skeletal muscles (29g)

When the net antianabolic effect is present, some of the resultant excesses of amino acids are converted to glucose following removal of the NH_2 group in the liver with subsequent increased urinary excretion of nitrogen (29c, e) The degree of this gluconeogenesis depends of course upon the particular amino acids present, and occurs in accordance with the outline in Chapter 1

2. Changes in Lipid Metabolism. The oxysteroids have been shown to increase the gastrointestinal absorption of fats in patients with steatorrhea of the sprue type (30a–c) In normal subjects the assimilation of fats is all but complete and hence further increase as a result of steroid excesses would be negligible, if present (31) It might also be pointed out that in adrenocortical insufficiency of the Addison's type steatorrhea is not a clinical symptom, though quantitative studies on fat excretion are lacking

The administration of oxysteroids and, to a lesser extent, of ACTH alters the serum lipid levels In some of the early studies in control subjects a uniform decrease in cholesterol was noted following ACTH and it was suggested that this represented utilization of this lipid for adrenal steroidogenesis (32a) In subsequent investigations in humans and in animals the bulk of the reports indicate that oxysteroids and ACTH in pharmacologic dosages usually increase the level of serum cholesterol, of phospholipids, and of fatty acids with a drop in neutral fat (32b–h) An initial hypocholesterolemic effect may be present (32a, f), with continued therapy this effect tends to decrease (32f) These changes in the serum lipid levels can perhaps be interpreted as representing part of the process of the mobilization of fat from tissue stores with a lag in storage and in disposal by the liver and at other sites (32c, i)

There is also evidence that the intermediary metabolism of lipids is modified by steroid therapy It has been noted that these agents decrease ketone body formation (33a–i) This is certainly in part a result of the well-known glycogenic effect of oxysteroids (17f, j), since it has been amply demonstrated by Mirsky *et al* (15) that deglycogenation accentuates ketosis while reglycogenation minimizes it Other factors however may also be operative The work of Kinsell *et al* with diabetic patients maintained on carbohydrate-free diets of protein and fat indicates that gluconeogenesis is greatly increased beyond that possible from the amino acids (33a c, d, f) This points to a transformation of fatty acids to glucose and therefore represents a decreased conversion of fat to acetoacetic and beta hydroxybutyric "ketone bodies" Possibly oxysteroids have such an effect The lessened ketosis after oxysteroids is a variable matter depending

on the experimental conditions (34) but it cannot be attributed to a greater ketone body disposal since they disappear at usual rates when administered (34) It may be however that other deviations in fatty acid metabolism are induced by oxysteroids

It has already been noted that the fatty acids and glycerol which are set free by oxysteroids are converted to glucose via gluconeogenesis The remainder of the released lipids are either utilized directly in the tissues or redeposited centripetally In patients the net effect of this last process is a remoulding of body contours of the type seen in Cushing's syndrome, resulting in thin and even spindly extremities and a bulky trunk, a fat pad overlying the lower cervical vertebrae (the so called buffalo hump), a rounding of the cheeks (referred to as the moon face), and a stretching of the lower abdomen and other parts of the trunk with formation of striae These striations, in contrast to those seen in ordinary obesity or in pregnancy, assume a purple hue as a result of dilatation of vessels and extravasations of blood

The seborrhea and acne which almost always develop with continued 11-oxysteroid therapy should be mentioned under the subject of lipid changes, even though androgenic steroids probably play the major etiologic role This overlap of adrenocortical steroids in their effects is true in other respects We have already referred for example to the overlap of the mineral regulating steroids, such as DOC and aldosterone, and of the 11-oxysteroids in affecting the retention of sodium and the excretion of potassium

3. The Carbohydrate Effects of the 11-Oxysteroids It is evident from the preceding two sections that the 11-oxysteroids accelerate the new production of glucose from protein and from fat This presents the organism with an increased carbohydrate load The glycosuria which results must be differentiated from the renal glycosuric effect of adrenocortical steroids (33g–i)

a Mechanisms of Carbohydrate Intolerance Following Adrenocortical 11-Oxysteroids It is theoretically possible that 11 oxysteroids interfere with carbohydrate metabolism by accelerating the destruction of insulin, by blocking the penetration of glucose into cells by interfering with the ATP mediated phosphorylation of glucose, by impeding the disposal of the phosphorylated hexose via glycogenation glycolysis, or the hexose monophosphate shunt, by blockade in the Krebs cycle itself, or by slowing the new formation of ATP which is achieved via the Krebs cycle As an alternative it may be that disposal remains virtually intact (34b, c) while gluconeogenesis presents a carbohydrate load which exceeds the capacity for disposal Finally, a combination of impaired disposal and increased carbohydrate load may be present The data indicate the last of these to be

the most likely explanation (35a–f 36a–d) The work of Elgee *et al* (35a, b) clearly suggests that the impairment of carbohydrate metabolism by 11 oxysteroids is not mediated by accelerated destruction of insulin as a result of excesses of growth diabetogenic factor

The studies of Levine *et al* with adrenalectomized eviscerated animals maintained with or without insulin indicate that oxysteroids do not discernibly influence the volume of distribution and hence the entry into cells of exogenous hexose in such preparations (37) From this they conclude as others have done (23a) that the disturbances in carbohydrate metabolism produced by oxysteroids in intact animals have their site of origin and action largely in the liver However the studies of Bornstein and Park (38) and Stadie *et al* (35e) show that *in vitro* the uptake or utilization of glucose by rat diaphragms may be inhibited under specific experimental conditions

Evidence is also available that these hormones do block the utilization of glucose in tissues at an unidentified point in the citric acid cycle pyruvate levels increase (39a b) and citric acid formation decreases (40) This may be an anti insulin effect exerted at the Krebs cycle or elsewhere in keeping with the fact that experimental animals become extremely resistant to the lethal hypoglycemic effect of insulin when maintained on 11 oxysteroids (41)

The early work of Conn *et al* with ACTH (42a b) suggested that the administration of glutathione ameliorated the hyperglycemia and glycosuria produced by this hormone in a healthy volunteer This was attributed to possible conversion of an alloxan like metabolite to nondiabetogenic dialuric acid in the presence of glutathione Others have also suggested that the availability of sulfhydryl groups from glutathione protected the islet cells in the pancreas (42c d) Subsequent work however has indicated that glutathione may not decrease after oxysteroids (42e f) and that the carbohydrate intolerance which develops (42g h) can be related to prolongation perhaps of cortisone survival

Irrespective of the actual mechanisms involved the fact appears to be that the organism receiving 11 oxysteroids is incapable of disposing of glucose as readily as normal at the same time that the carbohydrate load is increased through gluconeogenesis The resultant increased demand for insulin is evident in the degranulation and glycogen infiltration of the beta cells of the pancreas (42i)

b Glycogenating Effects of Oxysteroids Two important prerequisites for deposition of glycogen in the liver are the presence of adequate or even excessive amounts of carbohydrate and sufficient insulin Both of these conditions are met in the subject receiving 11 oxysteroids despite the anti insulin effects which have been described and glycogen is therefore

laid down As a matter of fact this is such a characteristic feature of 11-oxysteroid action that it has been employed, as mentioned earlier (17a), in adrenalectomized mice as a bioassay technique for 11-oxysteroids of natural or synthetic origin

c Carbohydrate Changes in Patients Receiving Oxysteroids Despite the increased gluconeogenesis and the evidences of some type of insulin blockade, animals and patients receiving ACTH or 11-oxysteroids are almost always able to dispose of carbohydrate loads without evidence of undue hyperglycemia and glycosuria However measurements of the glucose assimilation coefficient indicate that quite regularly the peripheral disposal of glucose is initially diminished by cortisone (43a, b) The occasional development of clinical diabetes mellitus during steroid or ACTH therapy probably represents the unmasking of a latent tendency to diabetes (43c–f, 44a–e) In our experience based on the therapy of a total of more than 300 cases of rheumatic carditis, nephrotic syndrome, and other diseases in children and in adults with cortisone or ACTH we have seen *but four cases of diabetes mellitus appear* (see figure 3-2 and table

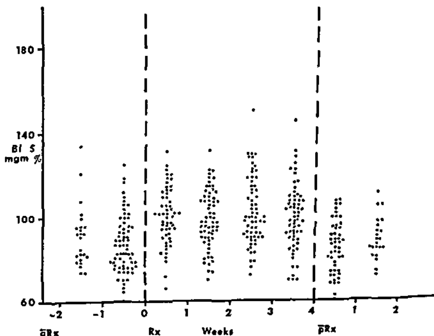


FIG 3-2 FASTING VENOUS BLOOD SUGAR LEVELS IN NEPHROTIC CHILDREN

ase
1 of

ACTH (43e, f)

TABLE 3 II

Occurrence of diabetes in patients under care of author and his colleagues while receiving ACTH or adrenocortical steroids

Disease State	Age Group	Therapy	No of Treatment Courses	Development of Diabetes	Ref
Rheumatic fever, initial attack	Children	Cortisone 300 mg q d 6 wk, decr to zero 6th–8th wk	55	Zero	43c, d
Rheumatic fever, recurrent attacks	Children	Cortisone 300 mg q d 6 wk, decr to zero 6th–8th wk	53	Zero	43f
Nephrotic syndrome	Children	ACTH 100 mg q d 28 d	30	Zero	43e
Nephrotic syndrome	Children	ACTH 100 mg q d 28 d	106	One	43f
Nephrotic syndrome	Adults	ACTH 200 mg q d 28 d	34	One	43f
Lupus erythematosus disseminatus	Children	Cortisone 100–200 mg for 12 mo or longer	7	Zero	43f
Lupus erythematosus disseminatus	Adults	Cortisone—up to 1 gm/day c̄ or s̄ ACTH for months or years	9	One	43f
Pemphigus vulgaris	Adults	Cortisone—up to 1 gm/day c̄ or s̄ ACTH for months or years	3	Zero	43f
Scleroderma	Adults	Cortisone—up to 1 gm/day c̄ or s̄ ACTH for months or years	4	One	43f
Periarteritis nodosa	Adults	Cortisone—up to 1 gm/day c̄ or s̄ ACTH for months or years	1	Zero	43f

3-II (43e–f) The administration of these agents to known diabetics usually raises the insulin requirement (44f–h) (table 3-III) On the other hand, diabetics present in hirsute women may actually require a lower dosage of insulin during steroid therapy This happened in three cases reported by Bastenie *et al* (44i), while in five others the requirement rose

In some of the patients the recorded peak and the two hour level in glucose tolerance tests initially do show a rise above the pretherapy responses (45a b, 46a,b) Furthermore the electrolyte changes which ac-

TABLE 3 III

Effect of ACTH or steroid therapy on insulin requirement of juvenile diabetics

Patient	Age	Diagnosis	Therapy	Maximum Insulin Dosage	
				Before Rx	During Rx
			mg/d	u/d	u/d
J D	30	Diabetes mellitus + nephrotic syndrome	ACTH 200	40	60
J L	16	Diabetes mellitus + nephritis	ACTH 100	44	96
T B	10	Diabetes mellitus + rheumatic fever	ACTH 80, cortisone 300	52	145

company accelerated disposal of carbohydrate following insulin or glucose may be less marked (46a) than in control subjects, even when the blood sugar responses themselves are not altered

Insulin tolerance tests also show some impairment of response upon initial administration of ACTH or adrenocortical oxysteroids (46b) This appears to be less marked with ACTH (45a, 46c)

d Characteristics of "Steroid Diabetes" Wilder (47a), Bookman *et al* (44e), Forsham and his colleagues (47b), and others (47c, d) have pointed out the salient differences between spontaneous diabetes mellitus and that which follows ACTH or oxysteroid therapy, the latter is a) highly resistant to insulin, b) accompanied by losses of body protein, c) characterized by increased amounts of liver glycogen, d) more resistant to ketosis, e) more susceptible to fasting, f) present with other features of adrenocortical overactivity, and g) reversible after hyperadrenocorticism is corrected

e Transient Nature of Carbohydrate Disturbances Despite Continued Oxysteroid Therapy Just as the negative balances of nitrogen may become modified with continued therapy, there is evidence that the carbohydrate intolerance may be a transient phenomenon (26l) This has been reported by Bastenie *et al* (43a,b) It has also been noted that ultimately the patient may actually show an increase in carbohydrate tolerance while on ACTH or cortisone beyond that present prior to therapy This has been attributed to decreased production of endogenous steroids (43a, b) and is in line with the observations in certain hirsute diabetic women (44i)

It has also been suggested that prevention of potassium deficits or the use of potassium supplementation influences the carbohydrate disturbance (48a–d) and that sodium restriction benefits (48e) or aggravates (48a, d) decreased carbohydrate tolerances It will be recalled that attempts to

demonstrate an effect of potassium upon the negative nitrogen balances during ACTH cortisone regimens were similarly successful and unsuccessful

f Use of ACTH or Oxysteroids in the Therapy of Spontaneous Hypoglycemia This has been reported to be followed by control of symptoms and blood sugar levels in most but not all instances of the noninsulinoma type (49a–f)

C The Effects of Androgenic Steroids upon the Intermediate Metabolism of Foodstuffs

The androgenic steroids of adrenocortical or gonadal origin in pharmacologic dosage exert a protein anabolic action (50a–c) which leads to the deposition of nitrogen and electrolytes such as phosphorus and potassium in tissues They, in conjunction with estrogens, presumably determine the configuration of body musculature and size in the male, and the degree and distribution of body fat It has already been indicated that these steroids play some as yet unclarified role in seborrhea and acne The writer is unaware of any direct influence of androgens upon carbohydrate metabolism

D Adrenocortical Hyperfunction

In primary aldosteronism resulting from an adrenocortical tumor which is producing this mineral-regulating steroid one finds retention of sodium, deficits of potassium, alkalosis, defective renal excretion of water but no evidence of alteration in the metabolism of carbohydrate, fat, or protein (20f) This is in keeping with the fact previously discussed, that even though this steroid is of the 11-oxy type and does have glycogenic properties when given in pharmacologic dosages, it is not present in sufficient amounts, even in the case of tumor, to exert any detectable influence on the intermediary metabolism of foodstuffs

Patients with hyperplasia, adenomata, or cancers of the adrenal cortex which produce Cushing's syndrome changes do elaborate large amounts of 11 oxysteroids These induce marked alterations in the metabolism of foodstuffs with evidences of nitrogen wastage from muscles and bone, redistribution of body fat, and frequent but not invariable impairment of carbohydrate metabolism (24a, 47c, 51a–e)

We have no evidence that female patients with the benign form of virilization (increased facial hair, 17-ketosteroid output in the masculine range with a decrease upon cortisone therapy, and no evidence of pelvic or adrenal tumor) have any alterations in carbohydrate, fat, or protein metabolism (52) Glucose and insulin tolerances and electrolyte changes are within the usual range Glucose as well as insulin tolerance studies

in the adrenogenital syndrome of infancy and childhood have been either within normal limits or have revealed relative or absolute hypoglycemia (53a–i) In the latter instances the change is attributable to a deficiency of oxysteroids rather than to excesses of androgenic steroids

Summary

The medulla of the adrenal cortex elaborates epinephrine and nor epinephrine which produce hyperglycemia by deglycogenation of the liver and perhaps by blockade of the peripheral disposal of glucose Increased gluconeogenesis from fat and protein, and conversion of lactic acid set free from deglycogenation of muscle to liver glycogen or to blood glucose may also play a role

The 11 oxysteroids of the adrenal cortex of which hydroxy cortisone or compound F is the chief example alter carbohydrate metabolism by increasing gluconeogenesis from amino acids and perhaps from fats These compounds exert an antianabolic effect upon the incorporation of amino acids into tissue proteins, thereby providing a larger amino acid substrate for gluconeogenesis In addition, as in the case of diabetogenic growth hormone studies with rat diaphragms indicate that utilization of glucose for formation of tissue glycogen is diminished In the liver, however, the 11-oxysteroids facilitate the formation and deposition of glycogen and presumably thereby minimize the formation of ketone bodies despite the concomitant overproduction and under-utilization of glucose In experimental animals this steroid type of diabetes is accompanied by histologic evidences of beta cell injury and destruction On the other hand loss of adrenocortical function results in hypoglycemia by virtue of diminished gluconeogenesis, removal of the peripheral blockade of glucose utilization and diminished liver glycogen stores

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decreased utilization of foodstuffs most hypothyroid patients are not fat (4i), presumably because the illness interferes with the usual caloric intake In contrast to the hyperthyroid patient, serum lipids and cholesterol values are regularly increased in myxedema (4e)

C Upon Glycogen Stores

It has long been known that the administration of thyroxin for several days results in marked depletion of liver glycogen stores (3a, 5a–c) Muscle glycogen also diminishes (5d) This is a specific effect of thyroxin which cannot be cancelled even by high carbohydrate diets, and represents therefore a shift in the equilibrium which maintains the store of liver glycogen toward increased glycogenolysis or decreased glycogenesis

D Upon Glucose, Insulin and Epinephrine Tolerance Tests

Fasting levels of blood sugar in hyperthyroidism are probably not greatly different from normal, though adequate control data might support the contention voiced in the older writings that relative hypoglycemia is at times present (6a) The administration of glucose produces an undue hyperglycemia (6b–c) with a return to the usual 2- or 3 hour levels in most but not all subjects

The blood sugar responses following insulin administration or epinephrine injection probably depend in the main on the status of liver glycogen stores If these are adequate as in hypothyroidism, the response is indistinguishable from normal but may be augmented, if glycogen is depleted, as in hyperthyroidism, insulin evokes a greater degree of hypoglycemia and epinephrine results in less of a blood sugar rise (7a, b) In animals athyreosis decreases absorption and decreases peripheral utilization The fact that the disposal of exogenous carbohydrate is diminished in terms of tolerance curves after thyroidectomy indicates that the latter has the greater net effect (8a, b)

II. The Experimental Production of Diabetes Mellitus by Thyroid Administration

Houssay and his co workers (9a–c) have shown that in some partially depancreatized animals with islets reduced to one sixth or one-eighth of normal, hyperglycemia, glycosuria, and other evidences of diabetes can be precipitated by desiccated thyroid in toxic dosage, 0 5 to 2 0 gm

large amounts of exogenous thyroid do not produce any evidence of diabetes in an animal with an intact pancreas (9a), nor are they effective if

ven for several days only (9d) In such animals the ... islets of Langerhans may or may not be morphologically ... the partially depancreatized animals which develop the ... alinization, and other evidences of islet damage are ... (9a) The studies of Fraenkel Conrat *et al* (9e) indicate ... creases the insulin content of the pancreas This suggests ... tes which develops in the partially depancreatized animals ... n exhaustion of the islets Houssay (9b) in 1945 interpreted ... s the result of a combination of alimentary hyperglycemia ... rect toxic action of the hormone on the pancreas

Molander and Kirschbaum (9f) have employed alloxan ... monstrate the diabetogenic action of exogenous thyroid ... rst received alloxan in amounts insufficient to produce ... quent administration of desiccated thyroid for a period of ... roduced the diabetic syndrome together with lesions of ...

From the above studies it is clear that thyroxin or thyroid ... an produce ultimately but not immediately, damage ... f the remaining insulinogenic portion of the pancreas ... ancreatized or incompletely alloxanized animals but that ... sult only in a reversible lesion

III Spontaneous and Induced Hyper- and Hypothyroidism in Human Diabetes

The Occurrence of Diabetes in Hyperthyroidism ... thyroidism in Diabetes

In contrast to the definitely greater incidence of diabetes ... cromegaly or Cushing s syndrome due to excessive anterior ... lrenocortical activity, respectively there was at one time ... hether the frequency of clinical diabetes is higher in patients ... yroidism

Joslin and Lahey (10a) in 1928 reported 43 instances of ... yroidism in 4917 diabetic patients Andrus (10b) reviewing ... ries at Johns Hopkins a few years later found three ... oth diabetes and hyperthyroidism in a series of 200 ... ve cases of hyperthyroidism among 400 diabetics He ... oslin and Lahey that the coincidence of hyperthyroidism ... no greater than the incidence of diabetes in any ... atients However, as more precise indices of hyperthyroidism ... eveloped and as experience has increased, it has become ... etes does actually occur more frequently in the hyperthy... nd that diabetics are more apt to develop thyroid overa... he data of Regan and Wilder (10h) based on 1882 patie...

thyroidism of whom 3 2 per cent had diabetes suggest that the type of hyperthyroidism is a determining factor Thus in the exophthalmic goiter group 1 7 per cent had diabetes while in the toxic adenoma category 5 6 per cent developed diabetes They suggest that the higher incidence in the latter may be attributable to the longer duration of untreated thyroid overactivity

B The Simultaneous Occurrence of Diabetes Mellitus and Spontaneous or Induced Myxedema

In some of the earlier clinical reports it was suggested that thyroid underfunction protected the patient against the development of diabetes (11a) This was in all probability a premature and invalid conclusion though substantial statistical support of the type present for hyperthyroidism is lacking Certainly it is amply clear that the two entities can and do occur in the same individuals (4i, 11b–n), even though the actual incidence has not been defined The possibility exists that the lessened rates of absorption from the gastrointestinal tract and the decreased intake present in myxedema have a beneficial effect upon the regulation of the diabetic It has also been reported in a very small number of patients that total thyroidectomy in diabetics without antecedent thyroid disturbances *facilitated the control of diabetes (11o–q), though the myxedema* thereby induced was of itself troublesome

C Aggravation of Pre-Existent Diabetes Mellitus by Spontaneous Hyperthyroidism and its Amelioration

There is ample evidence that the development of hyperthyroidism in a patient with diabetes mellitus aggravates the carbohydrate disorder and raises the insulin requirement (12a–d) Diabetic coma and thyroid crises have even occurred simultaneously (12e, f) Conversely, the control of hyperthyroidism or the production of myxedema as a result of surgical or medical therapy generally (12a–d), but not always (12g), ameliorates the diabetes There is some suggestion that this effect is more readily achieved in toxic adenomata than in exophthalmic goiter (12h–j) which *presumably originates in the pituitary gland*

D Effects of Thyroid or Thyroxin Administration to Diabetic Children and Adults

It has been shown that the administration of sodium l-thyroxin in amounts sufficiently in excess of endogenous production of this hormone raises the basal metabolic rate and the level of circulating protein bound iodine in animals as well as in humans (13a–f) In these two regards therefore such regimens duplicate clinical hyperthyroidism However such ad

ministration of thyroxin to diabetic children and adults in our clinic and hospital population has been shown to have no *immediate* effect upon the insulin requirement as reflected in quantitative and qualitative urine sugar analyses (table 4 I) (13d) Chronic or continued thyroid or thyroxin therapy does however aggravate the intensity of clinical diabetes (figure 4 1 taken from our unpublished studies) In alloxan diabetic animals an amelioration of hyperglycemia has been noted during the first month of thyroxin therapy with increased glycemia thereafter (13g) It is therefore clear that this hormone does not have a prompt anti insulin effect of the type exhibited by the diabetogenic growth factor of the anterior pituitary or by certain of the adrenocortical steroids

IV How Does Hyperthyroidism Aggravate Diabetes?

A number of the older and current workers have expressed the view that the deleterious effect of hyperthyroidism upon diabetes is nonspecific (11l, 12a, 14) and related perhaps to the total energy exchanges Our own data presented in table 4 I indicate that the well established deleterious effect of hyperthyroidism upon diabetes mellitus must represent a sequel to the hypermetabolic or other effects of thyroxin This is in keeping with the absence of immediate effects and their presence after continued or chronic therapy Such a sequel could be the result of the net metabolic action of thyroxin or it might represent the effects of partial starvation Other possibilities include inadvertent overinsulinization of the hyperthyroid diabetic or some ultimately deleterious influence upon the intermediate metabolism of glucose mediated through disturbances of enzymes such as hexokinase insulinase anti insulinase phosphorylase etc

A Possible Aggravation of Diabetes as a Consequence of the Net Meta-bolic Effect of Thyroxin

Thyroxin is known to accelerate glucose catabolism in tissues bo[illegible] *in vitro* and in the intact animal (2a–d) One would expect that if th[illegible]

deglycogenating effect upon the liver even when carbohydrate [illegible] is high (3a 5a–e), and b) it increases gluconeogenesis from body [illegible] (3a–d) The first of these makes more difficult the regulation of the dia-betic, since liver glycogen stores are not available to cover the [illegible]istered insulin between periods of food intake The second o[illegible]genic action of thyroxin raises the load of carbohydrate pre[illegible] to the diabetic organism for disposal Hence, the deleterious effect of [illegible] of thyroxin in the diabetic might be explicable by a predomin[illegible] of the

TABLE 4 1

Diabetic children receiving sodium salt of L thyroxine 1 2 mg daily for 9 days with and without concomitant administration of compound S, F, or L (13d)

Subject	Age	Sex	Body wt	Duration of diabetes	Diet		Insulin dosage*	Serum PBI before Rx	Therapy	
					P F C	Calories			Thyroxine	Steroid
			kg					γ/100 cc		
R K	16	M	61 8	5 yr 3 mo	122 125 260	2631	P18R34→P16R38	3 5	1 2 mg /q d /9d	—
K R	15	M	61 8	3 yr 10 mo	115 125 330	2905	P18R54→P18R56	6 1	1 2 mg /q d /9d	—
R S	13	F	44 8	4 yr 1 mo	172 158 461	3954	P27R60→P27R70	5 6	1 2 mg /q d /9d	—
R V S	14	M	52 0	3 yr	135 145 275	2955	NPH62R6→NPH74R6	7 9	1 2 mg /q d /9d	—
C L	11	F	34 2	6 yr 4 mo	120 100 250	2380	P10R28→P10R36	5 6	1 2 mg /q d /9d	Cpd S, 200 mg /q d /9d
R C	15	M	59 6	13 yr 5 mo	135 110 300	2730	P12R54→P14R56	4 1	1 2 mg /q d /9d	Cpd S, 200 mg /q d /9d
G P	15	M	43 2	5 yr 1 mo	120 100 250	2380	P10R27→P12R30	4 3	1 2 mg /q d /9d	Cpd S, 200 mg /q d /9d
J B	13	M	31 6	7 yr	125 100 275	2500	P16R28→P30R56	4 6	1 2 mg /q d /9d	Cpd F, 200 mg /q d /9d
D McA	16	F	58 2	2 yr	75 115 150	1935	P22R55→P36R82	2 8	1 2 mg /q d /9d	Cpd F, 200 mg /q d /9d
J D	13	F	48 8	3 yr	125 135 260	2755	P18R42→P22R75	3 8	1 2 mg /q d /9d	Cpd L, 200 mg /q d /9d

* P = protamine, R = regular

deglycogenating and gluconeogenic action over the peripheral catabolic effect

B Partial Starvation as a Possible Cause of Aggravation of Diabetes by Hyperthyroidism

DuBois (4a) has shown that in hyperthyroidism there is a one and one half to two-fold increase in total caloric expenditure If the diet of a hyperthyroid diabetic is not increased in these proportions semi-starvation develops Under such circumstances the control of carbohydrate metabolism becomes more difficult (15a, b)

C Overinsulinization as the Cause of Increased Insulin Dosage in the Hyperthyroid Diabetic

It has already been pointed out that in hyperthyroidism glucose and other sugars, as well as fatty acids such as oleic, are absorbed more rapidly from the gastrointestinal tract This is attributable in part to a

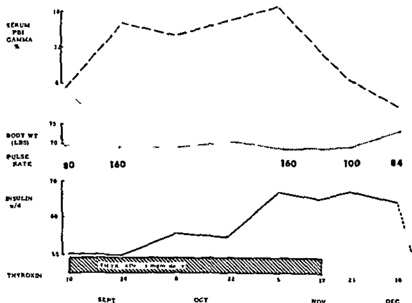


Fig 4-1 Increase in Insulin Requirement Following Prolonged Therapy With Thyroxin

In this 15-year-old juvenile diabetic the daily ingestion of 1 0 mg of sodium l thyroxin increased the insulin requirement from 50 units to 68 units per day concomitant with a production of tachycardia and a rise in the serum protein-bound iodine The rise in insulin dosage persisted for several weeks following withdrawal of thyroxin and then returned to pretherapy levels (unpublished data)

lar interest since the diabetes was aggravated at each menstrual period and ameliorated by large amounts of estrogens Others have since voiced the opinion that in their patients such beneficial responses have been produced (17m–o) The most interesting of these series is McCullagh's (17o) consisting of six acromegalic diabetics Estrogen therapy not only improved the diabetes clinically and, in five patients, in terms of the glucose tolerance response as well, but also controlled the acromegaly as reflected in a lowering of the elevated serum inorganic phosphorus levels and decreases in hand and foot size

These isolated observations do suggest that there may be clinical support for a beneficial action in diabetes of large amounts of estrogens and the aggravating effect of small dosages It is probably premature to consider this evidence conclusive because of the difficulties of clinical experimentation in a group of patients where many variables other than estrogen administration are undoubtedly operative One might cite among these the "placebo effect," and the natural tendency of newly discovered diabetes to ameliorate

Summary

Thyroxine and presumably triiodothyronine facilitate the peripheral disposal of glucose, deplete the liver of glycogen, and increase gluconeogenesis The production of experimental diabetes in partially depancreatized or incompletely alloxanized animals and the aggravation of preexistent diabetes in humans by excesses of thyroid hormone are well documented It is obvious in view of these circumstances that the enhancement of glucose utilization by thyroxine in tissues is of insufficient degree to overcome the effects of glycogen depletion and increased gluconeogenesis Additional factors which may play a role in the intensification of clinical diabetes by thyroid overactivity include an increased metabolic turnover or a starvation effect (depending on whether the diet is increased or fixed), the increased absorption of glucose from the gastrointestinal tract and by the renal tubules, and the development of inadvertent over insulinization, and increased destruction of insulin Correction of hyperthyroidism or the induction of hypothyroidism in previously euthyroid diabetics ameliorates the intensity of the diabetes

Estrogens in small amounts can aggravate diabetes while the administration of larger amounts may decrease hyperglycemia and insulin needs

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CHAPTER 5

The Production of Diabetes by Glucose and by Chemical Agents

The work based on extirpation of the anterior pituitary adrenal cortex thyroid or gonads and the injection of their products reviewed in the preceding three chapters has served to identify some of the conditions under which these endocrines influence carbohydrate metabolism In seeking possible nonendocrine diabetogenic agents it was logical to test first the effects of large glucose loads Pancreatic islet damage was thereby produced Later the finding of blood sugar changes following the administration of alloxan (a compound related to the purines and pyrimidines in

acid and dehydroascorbic acid which contain chemical groupings re

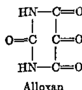
ings may represent therefore another type of experimental diabetes induced by organic chemicals Within the past five years a further group of compounds the fluoroacetates has been employed successfully to produce hyperglycemia and some of the other manifestations of diabetes These act within the Krebs cycle producing a block at the aconitine and segment. Finally other chemical agents such as neutral potassium ... and magnesium salts which may or may not fit into any of the above categories have been found to produce experimental diabetes

The characteristics of these various types of experimental diabetes will be reviewed prior to an evaluation of their probable role if any in the production of diabetes mellitus which appears spontaneously in humans

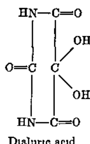
I The Use of Glucose as a Diabetogenic Agent

In 1938 Woerner (1a) reported that infusions of glucose produced lesions in the pancreatic islets The subsequent studies of Lukens Dohan and coworkers (1b-d) and others (1e f) established that the per... or intra-

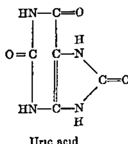
venous infusion of glucose to intact cats sometimes produced permanent hyperglycemia with evidences of initial hyperplasia and subsequent hydropic degeneration of the islet cells The last of these changes is more accurately referred to as glycogen infiltration in accord with the tenets of Duff and Toreson (1g h) and may be followed by ultimate destruction of the islets Subtotal pancreatectomy or pretreatment with alloxan in amounts insufficient to produce diabetes by itself potentiated the action of glucose (1c–f) Therapy with insulin instituted before the end of three months but not later, permitted islet recovery and was followed by disappearance of the diabetes (1c d) It was felt that the degree of hyperglycemia was an important determinant of islet damage These investiga



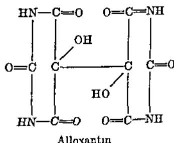
Alloxan



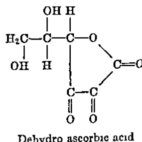
Dialuric acid



Uric acid



Alloxantin



Dehydro ascorbic acid

FIG 5 1 CHEMICAL STRUCTURE OF ALLOXAN AND OF OTHER COMPOUNDS

tions clearly established that infusion of glucose could be productive of diabetes

II. The Diabetogenic Action of Alloxan and Closely Related Compounds

A Mechanism of Diabetogenesis

Alloxan, the first of the laboratory organic chemicals with diabetogenic properties, was shown by Jacobs in 1937 to produce a transient hyperglycemia which was then followed by hypoglycemia (2a) His observations of the blood sugar curves were limited to 24 hours The ultimate hyperglycemia which makes up the end stage of the multiphasic blood sugar response to alloxan (see section B of this chapter) and results in permanent diabetes mellitus was reported four years later by Dunn and McLetchie and their colleagues (2b c) (figure 5-2) during a search for agents which would produce lower nephron nephrosis, *i e*, acute tubular damage Islet damage was observed in these rats This and the blood sugar effects were promptly confirmed by Bailey *et al* (2d e) in rabbits and rats and by Goldner and Gomori (2f) in dogs Subsequent studies have established the existence of species differences and defined the parameters of effective dosage schedules (2g k)

1. Factors Which Modify the Response to Alloxan A host of other variables which modify the response to alloxan has also been identified a) the sulfhydril grouping —SH, as in glutathione, cysteine and other compounds, and agents such as BAL which convert the —S—S group to —SH protect against diabetes if given prior to, during, or within a limited period after alloxan (3a-m), b) a high protein diet, perhaps by providing —SH groups (4a) the administration of glucose and certain other mono saccharides (4b-d), or a high intake of fatty acids (4e) also decreases the diabetogenic effect, c) sodium deficiency and perhaps potassium excesses potentiate the action of alloxan (5a-c), d) compounds such as nicotinamide the furans and combinations of nitrite and para-amino propiophenone have been shown to be protective (6a-d)

2. The Protective Action of Glutathione. Of this variety of protective and potentiating agents and regimens only the role of sulfhydril groups has been acceptably elucidated Lazarow and Patterson (3a-f) have pointed out that alloxan lowers the glutathione content of blood and tissues and that this interferes with the glutathione mediated conversion of alloxan to dialuric acid a nondiabetogenic derivative Alloxan can then cause direct injury to the cells perhaps by acting upon the —SH groups of enzymes and producing crucial metabolic blocks The pancreatic islets are presumed to be particularly susceptible to these toxic effects of alloxan be-



FIG 5 2 DESTRUCTION OF BETA CELLS OF PANCREATIC ISLETS BY ALLOXAN

Top photograph shows findings in the pancreas of an untreated rabbit, changes at bottom were obtained 16 hours following the administration of alloxan 200 mg per kg of body weight (from Dunn Kirkpatrick McLetchie and Telfer (2c) with kind permission of the authors & publishers)

cause the β-cell content of glutathione is lowered by the manufacture of insulin which involves the formation of —S—S— linkages from —SH groups The conversion of alloxan to dialuric acid and the relationship of the chemical structure of the latter to uric acid and alloxantin are shown in figure 5-1 Though dialuric acid, uric acid, and alloxantin have all been reported to be diabetogenic (7a-g) it is probable that diabetes occurs only when these compounds are converted to alloxan The fact that large amounts of these compounds must be used, that they lower the glutathione levels or are more effective in regimens which lower them, and that the results are sporadic are all in keeping with this view It has been shown that oxidized cytochrome C can effect the conversion in the case of dialuric acid (7h) Dehydroascorbic acid which is also diabetogenic (7i-p) bears some chemical resemblance to alloxan

B The Origins of the Blood Sugar Changes in Alloxanized Animals

It is probable that alloxan actually produces a four-phase change in blood sugar levels beginning with a hypoglycemia which appears in 15 to 30 minutes and is often masked or replaced by hyperglycemia (8a-d)

1. The Early Hypoglycemia: Role of Insulin. The studies of Gaarenstroom and colleagues (8e, f) suggest that the hypoglycemia which may *usher in the blood sugar changes following alloxan is dependent upon the* presence of a functioning pancreas and is probably due to a release of insulin

2. The Early Hyperglycemia: Role of Epinephrine and of Glucagon The hitherto so called initial hyperglycemia usually occurs within one to four hours of insulin administration and has been attributed to hepatic glycogenolysis (9a, b) This is supported by the absence of such a hyperglycemic phase in hepatectomized animals (8b) The demonstration that this is also true of adrenalectomized and adrenal demedullated animals (9c-e) indicates that alloxan probably induces a discharge of epinephrine which in turn activates liver phosphorylase It has also been suggested that this is mediated through a discharge of glucagon from the alpha cells of the pancreatic islets (8e)

3. The Late Hypoglycemia: the Indeterminate Role of Insulin. Between the fourth and tenth hours hypoglycemia reappears This has been attributed to a discharge of insulin from the damaged beta cells, but it has also occurred though not regularly (9d, 10a-d) in previously depancreatized animals Bhattacharya (9f) has postulated that blockade of liver glycogenolysis is responsible

4. The Late Hyperglycemia: Correlation with Beta Cell Damage. Hyperglycemia representing the third or fourth phase depending on whether or not hypoglycemia was initially manifest, reappears after the

tenth to twelfth hours in those animals in which diabetogenic amounts of the compound have been given This has been ascribed to destruction of the beta cells (2a)

C Intermediary Metabolism in Alloxan Diabetes

1. Fat. During the first week of the diabetes considerable ketosis pre vails without comparably high urinary glucose and nitrogen excretion (11a–c) This suggests an effect akin to or identical with starvation, though it may be more specifically related to alloxan induced metabolic changes with mobilization of body fat in excess of the catabolic and excretory capacities of the body and accumulation of ketone bodies Lipo genesis is actually decreased because of diminished glycolysis (12a–d) but cholesterol metabolism appears unimpaired (12a, b) In addition renal tubular injury with diminished excretory function (13) undoubtedly plays a role in the marked ketonemia cited above

2. Protein As renal function improves and as the diabetes becomes maximal the azotemia which occurs early after alloxan (13) disappears and urinary losses of various nitrogen compounds, phosphate, potassium, and glucose all increase (14a, b) Increased gluconeogenesis from body protein undoubtedly contributes to these urinary losses

3. Carbohydrate. The capacity to dispose of carbohydrate loads is decreased as a result of the insulin deficiency and the deposition of glucose as hepatic and tissue gl

mals indicate however

cycle is increased (15d

phosphate compounds are diminished in the liver and the activity of phos phatase and the metabolism of inorganic phosphate altered (16a–d)

In essence the modifications in energy transformations and the metabo lism of electrolytes, carbohydrate, protein, and fat, directionally at least, are those seen in any unregulated diabetic state irrespective of its etiology (see Chapters 18 through 20 on diabetic coma in humans)

III. Diabetogenic Effects of Chelating Agents

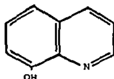
Kadota and colleagues (17a–c), Wolff *et al* (17d, e) Dell'Acqua and co workers (17f–j) and others (17k–t) have demonstrated that certain che

and related compounds,

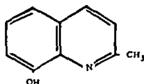
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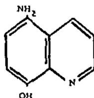
and diabetes in a manner reminiscent of alloxan Again species and indi vidual differences appear to influence diabetogenesis Kadota (17a) sug gested that the damage to the islets was related to a chelation and removal of the zinc which is known to be present in large amounts in these cells



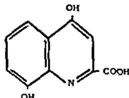
8 HYDROXYQUINOLINE (OXINE)
DIABETOGENIC



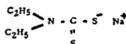
8 HYDROXYQUINALDINE
DIABETOGENIC



5 AMINO 8 - HYDROXYQUINOLINE
DIABETOGENIC



XANTHURENIC ACID
? DIABETOGENIC



SODIUM DIETHYLDITHIOCARBAMATE

FIG 5-3 CHEMICAL DIABETOGENIC AGENTS QUINOLINE DERIVATIVES AND SODIUM DIETHYLDITHIOCARBAMATE

(17p) In line with this there is evidence from the work of Wolff *et al.* (17 e, s) that the zinc actually decreases in the pancreas, and rises in the serum and urine of animals treated with thiocarbamate, changes that also occur ...

IV. Fluoroacetate Diabetes

others (18a–g) indicate that fluoroacetate administration results in formation of a toxic fluorocitrate which impedes or stops the citric acid cycle at the level of aconitinic acid (figure 1 5 in Chapter 1) Citric acid increases in the tissues (18c) In addition to the decreased utilization of ketone bodies there is increased production of ketone bodies

It is of interest that one of Engel s animals which developed permanent diabetes was found to have islet cell damage (18e) This is in keeping with the finding that pancreatic islet damage may occur either as a result of a direct toxic effect as with alloxan, or secondary to exhaustion as with glucose administration In fluoroacetate diabetes, if findings in this one animal can be duplicated, the islet cell damage would appear to result from the blockade in the Krebs cycle

V. Miscellaneous Agents Found to be Diabetogenic: Chromate, Magnesium, Glucagon

Mosinger *et al* (19a) have recently described hyperglycemia and islet cell damage in rabbits following the administration of neutral potassium chromate (K_2CrO_4) in 100 mg dosage on alternate days for 4 to 9 months At autopsy the animals also showed hyperplasia of the adrenal cortex, medulla, and thyroid The mechanism of this diabetogenic action of neutral potassium chromate is unknown but the attendant endocrine changes suggest an interesting alliance between a chemical effect and hormonal factors It should be remembered however that alloxanized animals also show adrenocortical hypertrophy (19b, c)

Baar (20) has used the terms amino acid diabetes in describing the concurrences of cystine crystals in the reticuloendothelial system and reducing substances in the urine This disturbance presumably falls into the larger category of renal tubular dysfunction of which the deToni Fanconi (20b–p) syndrome is one example (section C in Chapter 13) This subject was reviewed in detail by Elkinton and Danowski in 1955 (20q) The term amino acid diabetes should not be used since it suggests that amino acids cause diabetes

In 1905 Meltzer and Auer (21a) and Underhill and Closson (21b) observed that magnesium administration causes hyperglycemia and glycosuria in mammals Láng and Rigo (21c) then demonstrated in rabbits that magnesium chloride in small dosage lowered the blood sugar while larger amounts produced hyperglycemia Recently Suomalainen reported that following approximately 100 milligrams of magnesium chloride per kilogram of body weight hyperglycemia appeared in the hedge hog and in certain strains of laboratory rats and mice, but not in guinea pigs (21d)

Recently Best and his colleagues have reported that large doses of glucagon in oil are diabetogenic (22)

Summary

Glucose loading especially in partially depancreatized animals, leads to degranulation and ultimate destruction of beta cells and can result in permanent diabetes Chemical agents in the alloxan group (alloxan and at times alloxantin, uric acid, or dehydroascorbic acid) produce rapid beta cell injury and persistent diabetes The blood sugar response to alloxan is characterized by an early and later hypoglycemia with an interspersed hyperglycemic phase prior to the development of the permanent hyperglycemia Of the roles of various factors operative in this form of experimental diabetes that of glutathione has been most clearly elucidated This compound exerts a protective action, possibly by converting alloxan to dialuric acid a nondiabetogenic derivative A lack of —SH groups (which can be provided by glutathione) may be a crucial factor in determining injury to beta cells, since a —S—S— group is an integral part of the insulin molecule

Quinolines (including oxine) sodium diethyldithiocarbamate, diphenylthiocarbazone (dithizone) and sodium ethylxanthate can also produce beta cell destruction an effect which was initially attributed to chelation of zinc by these compounds Fluoroacetate diabetes is characterized by a block in the citric acid cycle, but islet damage has also been noted Diabetes can also be produced by chromate or magnesium salts and by glucagon

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others (18a g) indicate that fluoroacetate administration results in formation of a toxic fluorocitrate which impedes or stops the citric acid cycle at the level of aconitinic acid(figure 1 5 in Chapter 1) Citric acid increases in the tissues (18c) In addition to the decreased utilization of ketone bodies there is increased production of ketone bodies

It is of interest that one of Engel s animals which developed permanent diabetes was found to have islet cell damage (18e) This is in keeping with the finding that pancreatic islet damage may occur either as a result of a direct toxic effect as with alloxan or secondary to exhaustion as with glucose administration In fluoroacetate diabetes if findings in this one animal can be duplicated the islet cell damage would appear to result from the blockade in the Krebs cycle

V. Miscellaneous Agents Found to be Diabetogenic Chromate, Magnesium, Glucagon

Mosinger *et al* (19a) have recently described hyperglycemia and islet cell damage in rabbits following the administration of neutral potassium chromate (K_2CrO_4) in 100 mg dosage on alternate days for 4 to 9 months At autopsy the animals also showed hyperplasia of the adrenal cortex medulla and thyroid The mechanism of this diabetogenic action of neutral potassium chromate is unknown but the attendant endocrine changes suggest an interesting alliance between a chemical effect and hormonal factors It should be remembered however that alloxanized animals also show adrenocortical hypertrophy (19b c)

Baar (20) has used the terms amino acid diabetes in describing the concurrences of cystine crystals in the reticuloendothelial system and reducing substances in the urine This disturbance presumably falls into the larger category of renal tubular dysfunction of which the deToni Fanconi (20b–p) syndrome is one example (section C in Chapter 13) This subject was reviewed in detail by Elkinton and Danowski in 1955 (20q) The term amino acid diabetes should not be used since it suggests that amino acids cause diabetes

In 1905 Meltzer and Auer (21a) and Underhill and Closson (21b) observed that magnesium administration causes hyperglycemia and glycosuria in mammals Lang and Rigo (21c) then demonstrated in rabbits that magnesium chloride in small dosage lowered the blood sugar while larger amounts produced hyperglycemia Recently Suomalainen reported that following approximately 100 milligrams of magnesium chloride per kilogram of body weight hyperglycemia appeared in the hedge hog and in certain strains of laboratory rats and mice but not in guinea pigs (21d)

Recently Best and his colleagues have reported that large doses of glucagon in oil are diabetogenic (22)

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increases in blood glucose from hepatic glycogen but recent studies with oral insulin substitutes and with depot glucagon indicate that glucagon and phosphorylase effects may play a more important role in determining the severity of diabetes (see Chapters 11 and 16) Until recently, however, it has been generally agreed that loss of glucagon plays no role in the relative mildness of diabetes following extirpation of the pancreas It has been suggested that this is attributable, in part at least to the fecal losses of undi

sequent amelioration of the diabetes This is however only part of the answer since the diabetes remains mild even though undue losses of ingested foodstuffs are avoided by feeding pancreatic extract employing predigested food, altering dietary composition etc

2. The Incidence of Diabetes Following Subtotal Pancreatectomy in Animals. *Partial removal of the pancreas produces a loss of carbohydrate tolerance* in a variable percentage of the operated animals (4a–c) Removal of the tail and body is more apt to result in diabetes than is extirpation of an equivalent amount of tissue from the head of the pancreas (5a) This is presumably related to the relative number of islets present in these subdivisions of the organ The frequency of diabetes rises with the percentage of tissue removed but the results are sporadic Thus most but not all animals become diabetic when as much as 90 per cent of the islet tissue is ablated (5b) on the other hand evidences of carbohydrate impairment may occasionally appear after extirpation representing 50 per cent or less of the pancreatic mass Though some of this nonuniformity is ascribable to inadequacy of quantitative estimates and to functional impairment following interference with circulation etc it is likely that

presence or absence of the syndrome Thus forced feeding therapy desiccated thyroid, or administration of ACTH, cortisone or androgens each increases its frequency, whereas starvation propyl thiouracil feeding or estrogen therapy decreases it (1j, k 4a, b)

One can assume that in all animals rendered *permanently* diabetic by pancreatectomy or by subtotal pancreatectomy and adjuvants there is an absolute deficit of insulin secretion

3 The Low Insulin Requirement of Human Diabetes Which Follows Pancreatectomy. Complete removal of the pancreas by surgical means results in a relatively mild diabetes in patients Since this deprives the organism of lipase, trypsin and other enzymes, incomplete absorption of

foodstuffs or actual steatorrhea may also result However, it is noteworthy that subjects to whom carbohydrate is given parenterally or for whom an intake adequate to maintain weight is provided and assimilated the insulin requirement is low ranging between 15 and 50 units per day (6a h)

B Diabetes Which Follows Direct Chemical Injury of the Pancreatic Islets

1 Alloxan and Other Forms of Chemical Diabetes in Animals This is essentially a chemical extirpation of the islets occurring promptly upon exposure to adequate amounts of these agents If the dosage is not fully diabetogenic the animal may recover from a transient diabetes The syndrome may also develop with additional therapy or following carbohydrate loading thyroxin growth hormone ACTH or cortisone administration in animals given alloxan in subliminal dosage (7a) The disturbances in intermediary metabolism in the totally alloxanized animal are the same as those following pancreatectomy The insulin requirement is low and there is no change in insulin responsiveness It should also be pointed out that in alloxanized diabetic animals the question of inadequate absorption of foodstuffs cannot be raised inasmuch as the external secretions of the pancreas are intact

2 Alloxan and Other Forms of Chemical Diabetes in Humans Some workers have suggested that alloxan or related compounds may occur in humans in amounts sufficient to produce islet cell injury (7b) It is true that ample amounts of precursors such as uric and dialuric acids are constantly present but measurements usually reveal trace amounts or no alloxan (7c–h) This does not exclude the possibility of course that transient toxic levels may not be responsible at the onset of diabetes Neither is there any evidence that transient glutathione deficiency conducive to the production or maintenance of increased amounts of alloxan may not occur in humans (7i) The role of glutathione in minimizing or aggravating experimental alloxan diabetes is of course well established (7a)

C Diabetes Mellitus Following Upon Presumed Exhaustion of the Beta Cells

1 In Animals Dohan and Lukens and their colleagues (8a b) first

infusions thereby eliminating possible mediation through a nonspecific pancreatitis secondary to use of the intraperitoneal route Partial pancreatectomy prior to the injection of glucose intraperitoneally increased the incidence of diabetes Fructose which ultimately adds to the carbo

hydrate load, even though some may enter the glycolytic cycle without the mediation of insulin (see figure 1-3 in Chapter 1), has a similar action This is also true of galactose which is converted to liver glycogen and thence to glucose

This form of diabetes, like that which occurs in pancreatectomized or alloxanized animals, is mild and requires small amounts of replacement *insulin In addition it is reversible,* provided glucose infusions are stopped or insulin or phlorhizin is given before the pancreatic lesions become irreversible (8b)

2. In Humans. It may be that in humans *heavy loads of carbohydrate* or of foods, as in obesity, can produce similar islet exhaustion However though current or previous obesity is a frequent finding in adult diabetes, only five per cent of the obese population develop diabetes (1k, 8c), and obesity is rare in juvenile diabetics This last point is discussed in greater detail in Chapter 21 which deals with the growth and development of the diabetic child

In summary, therefore, it can be stated that the findings in pancreatectomized, alloxanized, or carbohydrate loaded animals clearly indicate *that the complete removal of insulin sources produces a diabetic state* which is uniformly mild Those cases of human diabetes which require little or no insulin *may therefore be,* and in the case of the pancreatectomized humans clearly are, clinical analogues of these types of experimental diabetes However in those instances of spontaneous human dia

D Growth-Diabetogenic Hormone Induced Diabetes

1. In Animals In terms of insulin action there is evidence that growth [illegible] the beta cells directly and exerts a definite anti in[illegible] [illegible] 1, 1, 9a-d) The ultimate effect is the [illegible] [illegible]le individuals of susceptible species The disturbances in carbohydrate metabolism may be present only during administration or persist after withdrawal of the growth hormone depending upon the degree of beta cell damage When growth hormone is withdrawn those *animals which remain diabetic* have the characteristics of depancreatized preparations In such animals the readministration of growth hormone intensifies the diabetes (9e), again establishing the presence of a diabetogenic action of this material beyond its effects on the islets

2 In Man. As pointed out in Chapter 2, trials of growth hormone in

dwarfs and other types of patients have not resulted in diabetes but neither has an unequivocal growth effect been elicited Insofar as an increase in growth-diabetogenic hormone as a cause of spontaneous human diabetes is concerned, it should be pointed out that diabetics are not giants (see Chapter 21 for data on children) nor acromegalics, that only a minority of the acromegalics develop diabetes (10a) and that when it appears it may be reversible (10b) (see also chapter 4, section V)

E ACTH or Steroid Diabetes

1. In Animals. This form of experimental diabetes is more difficult to produce than that which follows growth hormone, frequently necessitating subtotal pancreatectomy or therapy with subthreshold amounts of growth hormone as adjuvants When effected there is striking evidence of an anti-anabolic effect, increased gluconeogenesis from protein and fat, relative freedom from ketosis (11a), and a marked anti insulin action exerted at some unidentified point in intermediary metabolism (9a) The infrequency of ketosis *in ACTH or cortisone-induced diabetes is undoubtedly related* to the liver glycogenating effect of the 11 oxy and related adrenocortical steroids

2. In Man. Patients with Cushing's syndrome have a higher incidence of diabetes than the population as a whole but carbohydrate tolerance may be normal (11b) In patients receiving ACTH or cortisone, diabetes is an infrequent development (11c) It is probable that such susceptible individuals are prediabetic or actually diabetic on the basis of the heredity, obesity or illness The diabetes results from increased production of glu cose from protein and fat and, as cited earlier (9a), there is evidence of insulin blockade The glycogenic effect of the steroids tends to minimize ketosis and simplify regulation of the diabetes, even though the insulin requirement is increased The diabetes may disappear after withdrawal of the drugs

F Thyroid and Metathyroid Diabetes

1. In Animals The hyperglycemia and glycosuria occur only in animals prepared by partial pancreatectomy or incomplete alloxanization (12a) The ultimate exhaustion of the remaining function of the islets with loss of beta cells may be mediated, as indicated in Chapter 4, through increased intake, increased gluconeogenesis, liver deglycogenation, and insulin inactivation which exert a net effect greater than the facilitation of carbohydrate metabolism produced by excesses of thyroxin

2 In Humans. Though hyperthyroidism aggravates diabetes, most hyperthyroids are not diabetics, nor do most diabetics have hyperthyroidism (12b) Thyroid function is unaltered in juvenile diabetics, as reflected

in levels of serum protein-bound iodine (see figure 21-14 in Chapter 21) The data of Goddard and Sommers suggest that the secretory activity of the thyroid is increased in diabetes (12c)

G Lactogenic Hormone Diabetes

Data are too scant to characterize the mechanism whereby injection of this protein results in experimental diabetes in animals Studies to date in human diabetics certainly show no increase of gonadal function above normal (13a, b), if one looks upon lactogenic hormone as a gonadotropin

In summary of the data on hormonal agents in animal and in human diabetes it may be stated that even though anti-insulin effects have been demonstrated in animals in the case of growth diabetogenic factor and adrenocortical oxysteroids and may be responsible for the production or aggravation of diabetes by thyroid, gonadotropin, and gonadal steroid excesses, there is no evidence that any one of these factors is causally operative in each case of spontaneous diabetes in humans

II. Pancreatic Damage as a Common Denominator in All Known Types of Experimental Diabetes in Animals But Not in Man

A In Animals

Whenever it has been possible by means of one of the above chemical or hormonal agents to produce in animals either a transient or a permanent hyperglycemia and glycosuria (anterior pituitary extracts, growth and diabetogenic factor, and lactogenic hormone, adrenocortical 11-oxysteroids, desiccated thyroid or thyroxin following partial pancreatectomy), there has been evidence of a change in the pancreatic islets (1h) In the early phase this has consisted of degranulation of the beta cells believed to represent release of insulin, this is followed by a proliferative hypertrophic response in which acinar cells and even the ducts are converted to secretory epithelium (14a) This has been interpreted as an attempt to meet the organism's requirement for insulin In subsequent weeks or months the so-called hyalinization or hydropic degeneration of the islets appears which, as demonstrated by Duff and others (14b), is really glycogen infiltration, and there is a decrease in the size and number of pancreatic islets This marks the exhaustion phase which, if allowed to per- [illegible] of the islet tissue (14c) A [illegible] aracterizes [illegible] o intact or partially depancreatized animals (14a) On the other hand in the experimental diabetes which follows the administration of alloxan and related

compounds, of *chelators* such as *certain quinolines and thiocarbamates*, and, possibly of an enzyme poison such as fluoroacetate (14d), the pancreatic islet damage occurs far more rapidly, though again the ultimate histology is comparable to that seen with protracted hormonal therapy or prolonged glucose administration

This finding of an histologic common denominator has been taken by many to indicate that all forms of experimental diabetes are the same as that which follows pancreatectomy Though it is certainly true that in the hormonal, the glucose infusion and the chemical types, the animal is ultimately deprived of pancreatic islet function the question of how this comes about merits consideration It is quite possible that this common end result merely serves to mask a variety of different mechanisms which result first in relative and finally in absolute deficits of insulin, and that the final pancreatic damage is no more specific than the histologically uniform fibrosis which follows mechanical trauma burns, freezing toxic chemicals, etc

B In Humans

In contrast to the experimental forms of diabetes in animals in which pancreatic or beta cell damage is a common denominator islet changes are present in only a minority of human diabetics and there is considerable overlap between normal and diabetic tissues (15a–e) from the viewpoint of islet mass or extractable insulin Nonetheless, there is good histopathologic evidence in humans based on islet counts and measurements (15f), extraction of insulin from the pancreas (15g–j) and assay of insulin levels in urine (15k) that absolute deficits of insulin probably do occur in clinical diabetes even though the role of antecedent diet and of endocrinopathy, both established as important in animal studies (15l–v), has not been evaluated In the remainder one must postulate that a deficiency can exist without morphologic concomitants or that production is equal to or above normal but that ultimate effectiveness of the insulin is compromised It has already been indicated that there are no obvious signs that hormonal anti insulin factors play a role in more than a minority of diabetics The studies of Mirsky and others raise the possibility however that such a loss of effectiveness could be mediated through enzymatic destruction of insulin

III The Possible Role of Insulinase-Anti Insulinase Systems in Human Diabetes

The work of Mirsky and his colleagues (16a–k) and of others (17a–i 18a–d) has established the existence of tissue enzymes termed insulinases which degrade insulin Their action appears to be opposed by insulinase

inhibitors present in the liver and other tissues Mirsky has therefore proposed that diabetes mellitus of nonpancreatogenous origin may represent an excess of insulinases, a deficit of "anti-insulinases", or both This view is supported by his demonstration that human liver tissue obtained from diabetic patients at autopsy or by biopsy does at times have a low anti-insulinase titer

Final summary of possible interrelationships of human and experimental diabetes mellitus the diabetic syndrome which follows pancreatectomy in humans does resemble the carbohydrate disorder that can be produced in animals by extirpation or chemical damage of the islets, of the remainder of human diabetes, i e, the spontaneous type, only a few patients show features which suggest an analogy with experimental diabetes of the hormonal type and the rest do not Since at postmortem examination islet insufficiency is only an occasional finding, the disorder of carbohydrate metabolism known clinically as diabetes mellitus must represent various combinations of an absolute and at times of an insulin lack with an increased need for insulin, either because the amounts of this hormone available to tissues are inadequate, the metabolic load is increased, or both

A final cogent point is to be made in any comparison of human and experimental diabetes Vascular complications are rare in the latter (19a-f) but Becker and Friedenwald and their colleagues (19g) and others (19h, i) have produced lesions by means of 11-oxysteroid excesses resembling the nephropathy, retinopathy, and other lesions which appear in humans This subject is discussed in greater detail in Chapter 23

IV. Analogies Between Hereditary Obesity with Diabetes in Mice and Clinical Diabetes

In 1951 Mayer *et al* (20a–c) reported that a genetically obese strain of mice developed post prandial hyperglycemia and preferred a high fat intake drawing an analogy between susceptibility to diabetes and overweight in humans Subsequently studies in the same laboratory of fat synthesis in three types of experimental animals with obesity (genetic, gold thioglycolate, and hypothalamic) indicated that a decrease occurred in all on fasting but that this was least marked in the first of these (20d) Degranulation of beta cells has been found in this strain (20e) The role of a partial block in acetate metabolism in the hereditarily obese mice remains controversial (20f, g)

Summary

All the known forms of experimental diabetes (growth diabetogenic hormone, prolactin, adrenocortical oxysteroid, thyroid, estrogen, glucose,

alloxan, quinoline, dithiocarbamate, fluoroacetate, or pancreatectomy-induced) are characterized by injury, destruction, or removal of the insulin-producing cells of the pancreas Clinical diabetes may result from comparable total losses of endogenous insulin, from excessive destruction of insulin produced in normal or increased amounts, or from a combination of the two The mildness of the diabetes which follows total ablation of the pancreas in humans (even after the impaired absorption of foodstuffs as a result of deficient pancreatic secretions has been taken into account) points to an absolute deficit of insulin The need for replacement insulin is small The occurrence of clinical diabetes which necessitates greater amounts of insulin establishes the existence of anti-insulin factors In some patients these may be excesses of growth-diabetogenic factor or the other hormones cited earlier However, diabetes is not an invariable feature of acromegaly, Cushing's syndrome, hyperthyroidism, *etc*, nor is there evidence of excesses of such hormonal factors in the diabetic population as a whole The low correlation between hormonal factors and clinical diabetes makes the hypothesis of increased insulin destruction particularly attractive

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PART II

MANIFESTATIONS, DIAGNOSIS, AND THERAPY

CHAPTER 7

Incidence, Onset, and Heredity of Juvenile Diabetes

I. The Magnitude of the Diabetic Problem

A The Frequency of Juvenile and Adult Diabetes

There are about 150,000 Americans under the age of 15 who have diabetes mellitus, representing some five per cent of the total diabetic population This estimate is based upon the distribution of diabetics in the United States according to age in the surveys of 1935–1936 (1a–d), and 1947 (1e) The latter of these, conducted by the United States Public Health Service at Oxford, Massachusetts, indicated that in this sampling of 70 6 per cent of a community of almost 5,000 population there were 40 previously diagnosed and 30 previously unknown diabetics If the proportions in these two categories, totalling 1 7 per cent, are extrapolated to the population of the 48 states in the year 1956 there is a total of 2,800,000 known and unknown diabetics This number is to be doubled if the incidence rate recorded in Basel is employed (1f) Using 5 per cent for the incidence of this entity in children under the age of 15 a total of some 140,000 diabetic children is obtained Actually, the total of juvenile or formerly juvenile diabetics is more than twice this number since most of these patients survive into adulthood Furthermore, those who develop diabetes in the 15- to 20 year group might well be included among the juveniles The above figures are in line with calculations of most other workers (2a–c), though lower figures have been cited (2d)

The earlier study of DePorte (3a), the later ones of Gate (3b) and of Beardwood (3c), and the follow up of the Oxford Survey conducted in 1953 (3d) in which the later status of the members of the possible-probable diabetic group was determined all justify these and even higher estimates In the resurvey at Oxford, Wilkerson and Krall re examined some of these and found that of the group previously labelled borderline and not included among the diabetics, 14 4 per cent had developed diabetes mellitus, in contrast to a rate of 1 8 per cent in the control series The demonstration of the value of using blood sugar levels, either fasting or following some two hours after a meal, as a screening device for the detection of this disturbance of carbohydrate metabolism (3e–i) further supports the validity of the Oxford Survey

B Frequency of Diabetes in Relation to Other Childhood Illnesses

It is of interest to compare the magnitude of the juvenile diabetic population with the incidence of other childhood diseases During the past 10 years, for example, a total of 332 835 American citizens of all ages have been stricken by poliomyelitis (4a) The annual poliomyelitis attack rate in children under the age of 18 has ranged from 20,000 to 35 000 per year and hence this disease is somewhat more prevalent than is juvenile diabetes On the other hand diabetes is a lifelong disorder while recovery from poliomyelitis is often complete

Diabetes also occurs much less frequently than rheumatic fever Though reports vary (4b), one per cent of the school age children are believed to be affected with rheumatic fever or its aftermath Since all of the juvenile diabetics of the U S A make up but one twentieth to one tenth of the entire diabetic population (estimated at a little less than two per cent) it it obvious that in terms of total numbers diabetes is much less prevalent

C The Sex Incidence of Diabetes

It is known that in the adult form of diabetes the females outnumber the males (1b, e, 5a–c) and it is estimated that ultimately 4 per cent of the women and 2 per cent of the men develop diabetes (1b) The sex ratio appears to be approximately unity in the juvenile form (2b, c) In an unselected series of 595 of our patients, 309 were males and 286 were females, 51 9 versus 48 1 per cent (see figure 7-1) In some of the older studies where a consistent or a clear predominance of one sex or the other was present the total number of patients was small (5d)

D Mortality in Diabetics

It is to be noted that the total number of diabetics has increased in the intervals between the two USPHS surveys cited above (1a, e) Part of this rise in total numbers is attributable to population growth and part to earlier diagnosis and to the increased longevity of the diabetic as a consequence of more adequate therapy of complications such as infections (1c, 6a) It would be reassuring to find that a decreased mortality in diabetic coma contributes to the longer survival of these patients but specific figures in support of this have not been produced and this may well not be the fact (see Chapter 18)

1. Death Rates in the Entire Diabetic Population The mortality experiences in the diabetic population of this country in the last decade based on Bureau of Vital Statistics samplings corrected for a standard population (6b, c), are shown in tables 7-I through 7 III Diabetes at present stands eighth in the list of primary causes of death However the limitations inherent in such reports are well recognized by the Bureau

which issues them For example, even if diabetes is a contributing factor, the death is listed only under the primary disease (1c)

2. Mortality in Juvenile Diabetics. The mortality in diabetics under 15 has been falling during the past decade The death rate in 1945 in the 10–14 year old group was 1 7 per 100 000 of the standard population when 184 children died, in 1952 the deaths in this age group numbered 98 for an adjusted rate of 0 8 (table 7-II) (6b, c) Though specific causes are not obtainable from death certificates it is probable from the experience in other clinics (2a) as well as our own that many of these are fatal cases of coma

However, accidents, cancers including leukemia, acute infections, congenital malformations, major cardiovascular renal diseases including rheu-

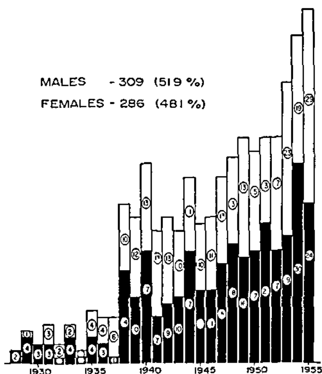


FIG 7-1 SEX INCIDENCE IN 595 JUVENILE DIABETICS

Males and females are present with about equal frequency in our group of patients The increase in new cases in 1938 followed upon the opening of a ward and clinic for diabetic children the second rise beginning in 1948 coincided with reorganization of the operation of these facilities under full time professional personnel Open columns identify females (seventh column from right, upper portion, should be 18 and not 13)

TABLE 7 I

Deaths of diabetics and crude death rates per 100,000 in relationship to the total mortality (1944–1954 incl)

Year	Ref and Source	Total Deaths	Deaths from Diabetes	Crude Death Rates	
				Total	Diab mell.
1944	6b *29* 19, 23, 1948	1,411,338	34,918	1,064 7	26 4
1945	6b *29* 19, 23, 1948	1,401,719	35,160	1,061 8	26 6
1946	6b *29* 19, 23, 1948	1,395,617	34,731	997 6	24 8
1947	6b *31* 125, 139, 1949	1,445,370	37,515		26 2
1948	6b *35* 325, 339, 1950	1,444,337	38,638		26 4
1949	6b *36* 239, 255, 1952	1,443,607	25,089	971	16 9
	38 68, 74, 1954				
1950	6b *37* 297, 317, 1953	1,452,454	24,419	963 8	16 2
1951	6b *40* 6, 12, 1954	1,482,099	25,047	966 3	16 3
1952	6b *40* 6, 12, 1954	1,496,838	25,474	961 0	16 4
1953	6b *42* 66, 1955	1,517,541	25,796	958 6	16 3
1954	6c	1,481,000	24,830	918 8	15 4

TABLE 7-II

Deaths and death rates of diabetic children in U S A in 0–14 age group

Year	Ref and Source		0–1	1	2	3	4	1–4	5–9	10–14	1 14	5–14
1945	6b *29* 19, 23, 1948	Totals	13					66	90	184		
		Rates	0 5					0 6	0 8	1 7		
1946	6b *29* 19, 23, 1948	Totals	14	19	15	12	15		58	124		
		Rates	0 6					0 6	0 5	1 2		
1947	6b *31* 125, 139,	Totals	28	22	14	15	12		60	115		
	1949	Rates	0 8					0 6	0 5	1 1		
1948	6b *35* 325, 339,	Totals	19	21	8	12	9		56	101		
	1950	Rates	0 6					0 4	0 4	0 9		
1949	6b *36* 239, 255, 1952	Totals	10	17	12	6	5		43	79		
	38 68, 74, 1954	Rates	0 3					0 3	0 3	0 7		
1950	6b *37* 297, 317,	Totals	23	14	10	9	5		57	79		
	1953	Rates	0 7					0 3				0 6
1951	6b *40* 6, 12, 1954	Totals	13	22	14	9	15		47	78		
		Rates	0 4					0 4	0 3	0 7		
1952	6b *40* 6 12, 1954	Totals	26	30	19	7	7		52	98		
		Rates	0 8					0 5	0 3	0 8		
1953	6b *42* 66, 1955										190	
1954	6c	Totals	30									

TABLE 7 III

Deaths from diabetes (totals and rates) in U S A 1945 1952 in various age groups

Year	15–19	20–24	15–24	25–29	30–34	25–34	35–39	40–44	35–44	45–49	50–54	45–54	55–59	60–64	55–64	65–69	70–74	65–74	75–79	80–84	75–84
1945																					
Totals	263	209		318	359		452	713		1230	2377		3775	5219		6079	5970		4482	2304	
Rates	2 4	3 3		3 5	3 5		4 6	7 6		14 4	30 2		55 7	96 4		149 3	ᐧ01 5		2		
1946																					
Totals	190	218		292	317		386	627		1147	2ᐧ08		3721	5086		6214	6141		4550		
Rates	1 7	1 9		2 6	2 9		3 8	6 6		13 3	27 8		53 5	93 0		149 7	202 9				
1947																					
Totals	174	270		289	310		428	682		1205	2355		4081	5603		6589	6535		5018	2618	
Rates	1 6	1 8		2 5	2 8		4 1	7 1		13 7	29 1		57 6	99 0		155 2	211 6				
1948																					
Totals	139	162		263	307		438	669		1187	2239		4080	5891		6828	8 91		5394	2814	
Rates	1 3	1 5		2 2	2 7		4 1	6 9		13 3	27 7		56 5	100 7		157 1	215 9		267 5	284 2	
1949																					
Totals	131	173		228	256		339	482		816	1498		2493	3603		4334	4402		3337	1997	
Rates	1 2	1 5		1 9	2 3		3 1	4 9		9 0	18 4		34 0	59 6		96 9	137 ı		160 0	191 7	
1950																					
Totals	126	122		256	255		359	539		773	1373		2288	3347		4255	4184		3464	2001	
Rates			1 1			2 2						13 4			42 4			100 3		166 7	
1951																					
Totals	111	154		268	258		352	504		794	1397		2277	3558		4324	4310		3511	2115	
Rates	1 1	1 4		2 2	2 2		3 1	4 8		8 6	16 6		30 8	57 6		86 0	119 9		154 7	177 0	
1952																					
Totals	104	166		274	316		366	509		787	1403		2226	3452		4474	4473		3529	2091	
Rates	1 0	1 6		1 9	2 7		3 2	4 8		8 3	16 5		29 5	54 4		87 3	120 2		160 2	171 7	

matic fever, and tuberculosis all precede diabetes as causes of death in childhood as shown in figure 7-2

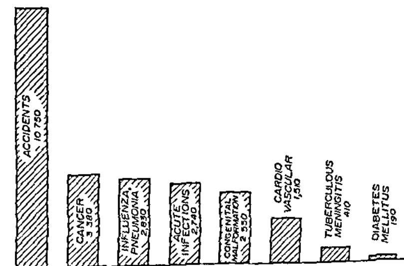
II. The Onset of Diabetes

A Interval Between Onset and Diagnosis

Colwell (7) has suggested that diabetes is a lifelong disease which begins to run its course at birth because the average insulin requirement at a particular age is ultimately the same irrespective of the age at onset This is primarily a philosophic rather than a biologic concept

1. In Children. It is quite likely that in children at least the clinical phase of the disease is usually detected within a matter of weeks of onset Thus in 405 of our children the average interval between clinical manifestations and diagnosis was *82* days, with a range of three days and *24* months (figure 7 3) In more than half of these children the diagnosis was made within 30 days or less of the onset of the symptoms If a higher index *of suspicion were maintained, this would undoubtedly be shorter*

2. In Adults. The experience in children is to be contrasted with the prolonged course of months or years without clinically disabling symptoms



(6c) are re-
deaths from
he preceding
kely though
the juvenile

through which an adult may pass unaware of the presence of the disease Beaser (8) estimates that only 34 per cent of adult diabetics admit to having classical symptoms at the time of diagnosis and 23 per cent deny any symptoms whatsoever With children however parents usually seek the opinion of a physician or clinic within days or weeks of the appearance of new complaints or signs

B Relative Frequency of Onset Symptoms

As in adult diabetes, increases in thirst, urination, and appetite are the most common symptoms but, as indicated earlier, they occur more frequently in juvenile diabetes In those of our group on whom detailed his tories are available they were present in one-half to three quarters of the children (figure 7-4) The reappearance of bedwetting is a frequent concomitant, being present in almost one half of this series One or more of these four manifestations were encountered in 9 out of 10 of these children In 93 of 513 children in our series the diagnosis was first made when the patient developed acidosis or coma This is in excess of the rate of ten per

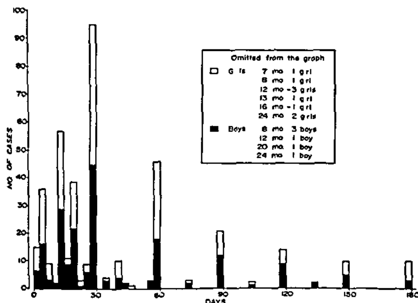


FIG 7-3 INTERVAL BETWEEN THE FIRST APPEARANCE OF SYMPTOMS AND THE DIAGNOSIS OF JUVENILE DIABETES

In 277 of 405 juvenile diabetics in our series the diagnosis was made within 30 days of the onset of the first symptom Considerable delay in diagnosis does occur, however in view of the 3 months which elapse on the average before the presence of diabetes is recognized

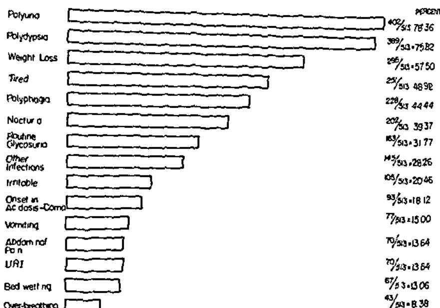


FIG 7-4 THE RELATIVE FREQUENCY OF ONSET SYMPTOMS IN 513 JUVENILE DIABETICS

Polyuria and polydipsia were present in more than three-quarters of our patients One or both of these symptoms were recorded in 89.5 per cent of the group Weight loss was not an invariable finding perhaps because polyphagia occurred in about one half of the children The high frequency of body weight loss and fatigability are to be remembered in the clinical interpretation of these nonspecific symptoms since about one-fifth of our juvenile diabetics have been dignosed only *after* acidosis or coma has appeared In our experience these are the patients among whom coma deaths are apt to occur

cent reported from some clinics (9a, b) ' . . . . . there (9c, d). *In another large segment of ou* nosis was based on a routine urine ana . include weight loss and irritability, in the order named These relative frequencies are in agreement with those in other published reports (2c, 9c, f)

C *Relationship to Respiratory and Other Infections*

It should be pointed out that a history of an antecedent infection, almost invariably respiratory in type, within several weeks of the onset symptoms, was obtained in 42 per cent of our juvenile diabetics John's figures are about as high (2c) *Though it is tempting to suggest that clinical* diabetes was thereby precipitated, and it may well be so, the great frequency of the common cold and less specific entities such as nasal discharge in the preschool and early school years established by the studies

of Dingle *et al* at Western Reserve (9g) makes this unlikely In the case of infections such as mumps, however, the subsequent development of diabetes could be related to specific injury to the pancreas (9h)

D Onset in Relation to the Time of the Year

The season of the year may or may not have a bearing on the appearance of the disease In figure 7 5 we have plotted the month of the year in which, in retrospect, the initial symptoms of the disease presumably appeared The highest frequency during any successive two months occurs during the winter As indicated above this may be related to the greater number of respiratory infections These figures agree with the limited experience of Adams (10a) but differ from those compiled by Baker (10b) and Spencer (10c) showing a lower rate of onset in the winter and a higher

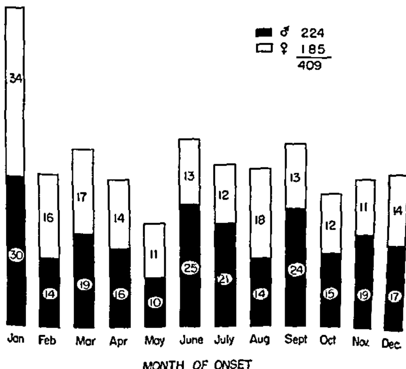


FIG 7-5 ONSET OF DIABETIC SYMPTOMS IN RELATION TO THE MONTH OF THE YEAR
In these 409 children in the Children s Hospital of Pittsburgh Series the symptoms of diabetes began most often in January This is more definite in the girls since amongst the boys June and September follow rather closely upon January as months of more frequent onset

one from April through September or October It is *conceivable that this* may be due to plotting the dates of diagnosis rather than the onset If this is tested in our own statistics, the peak months do not shift from winter toward spring (figure 7 6) It is probable therefore that these discrepancies *are to be* attributed to some inherent defect in sampling, such as insufficient numbers

E The Average Age of Onset of Juvenile Diabetes

The age of onset in our population is in line with that of other clinics (figures 7 7 and 7-8) (10d, e) The range of 4 to 12 years encompasses more than 60 per cent of the ages of onset and there may be peaking evident in the girls, as White *et al* have suggested (10d), at age 6 and again at or after age 10 In our series this peaking may be present in the boys as well as the girls, but the total numbers in each age group are small The mean ages of onset in boys and girls were almost identical, 8 and 7 years 10½ months, respectively.

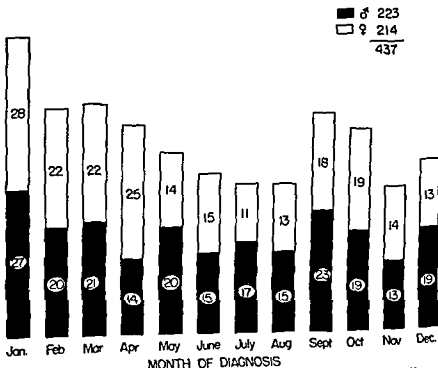


FIG 7-6 DIAGNOSIS OF JUVENILE DIABETES IN RELATIONSHIP TO THE SEASON OF THE YEAR In this group of 437 juvenile diabetics the diagnosis of diabetes was made more often during the fall and winter months (September to March)

III Heredity

There has been no unanimity of opinion on the genetic characteristics of diabetes mellitus It has been judged as recessive, dominant, or multigenic but the bulk of the evidence favors inheritance of the trait as a non sex linked recessive (11a–e)

A Incidence of Diabetes in the Families of Adult and Juvenile Diabetics

1 Family History in Adult Diabetics In diabetes which has its onset after maturity the familial incidence of the disorder ranges between 14 8 and 49 per cent (5a 11f) However an equally high family history of diabetes has been reported in a group of physicians who did not themselves have diabetes The incidence was 30 4 per cent consisting of 42 9 per cent in the Jewish and 20 per cent in the non Jewish members (11g)

2 Heredity in Juvenile Diabetes In juvenile diabetics as one might expect, the percentage of positive family histories rises with the duration of the diabetes Thus at the time of onset about two-fifths of our patients had a history of diabetes present on the maternal or paternal side if dis-

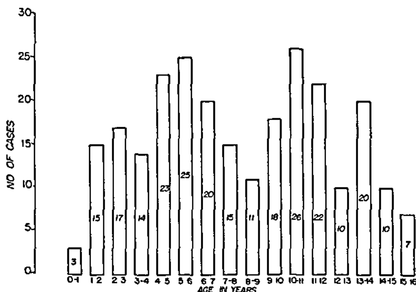
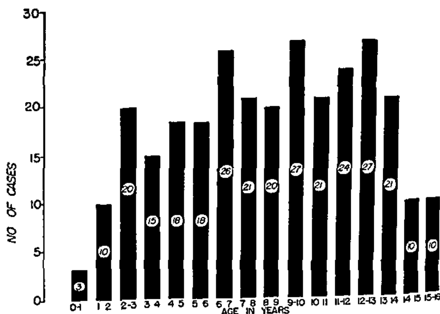


FIG 7 7 AGE AT ONSET OF DIABETES IN GIRLS (NOT AT TIME OF DIAGNOSIS)
In these female juvenile diabetics the initial symptoms of diabetes appeared at the average age of 7 years 10½ months The distribution curve suggests peaking between the fourth and seventh and again between the ninth and twelfth years This is in keeping with the findings of Wagner *et al* (10d)

tant relatives are included In figure 7-9 the details of family involvement at later inquiry of 220 juvenile diabetics and their families are summarized In this survey conducted after one to 15 years of known diabetes the incidence rose to 58 per cent This trend is in keeping with the general statistics and with those of White in particular (2c, 6a, 11h–k) The higher frequency in the later statistics is attributable largely to the appearance of diabetes in siblings and relatives more distant than the parents and not in the mothers and fathers of diabetics

3. Frequency of Diabetes Among the Children of Diabetics. In keeping with the concept that the diabetic trait is recessive (11l–o) White has reported that when both parents are diabetic 33 per cent of their offspring have diabetes and diabetic type of glucose tolerance tests are obtained in a total of 62 per cent of the children, if only one parent is diabetic, irrespective of whether it is the mother or father, nine per cent of the children have clinical diabetes with possible diabetes, judged by the results of tolerance tests, present in an additional 12 to 14 per cent (11p)



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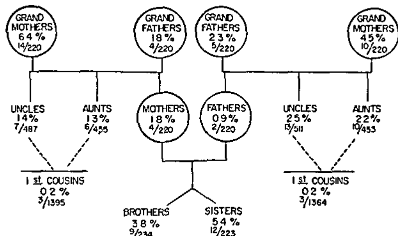


FIG 7-9 INCIDENCE OF DIABETES IN THE IMMEDIATE AND DISTANT RELATIVES OF JUVENILE DIABETICS

At the time of survey of the above group of 220 children in our series diabetes had been present up to 20 years with a mean duration of 4 45 years Among the immediate relatives (mother, father, grandparents uncles aunts first cousins and siblings) there were 84 diabetics The incidence was highest among the maternal and paternal grandmothers An additional 43 distant relatives were reported to be diabetic, resulting in a positive family history in almost 58 per cent of the juvenile diabetics. The excess of individual diabetics over the total of positive family histories reflects of course, the presence of more than one diabetic in the family tree of some of the children

B The Problem of Anticipation in Diabetes

A number of years ago Woodyatt and Spetz (12a), stimulated by an earlier summary by Naunyn (12b), reported that their studies of some 100 diabetic families indicated a history compatible with the so-called phenomenon of anticipation In this view diabetes makes its appearance in susceptible families at a progressively earlier age in successive genera-

cessive generation At times a generation was missed, resulting in a 40-year interval

1. Is Anticipation a Reality? Anticipation however is not generally accepted as a genetic phenomenon (12c–g) and its proponents appear to be in the minority The studies of Steinberg and Wilder (12e, f) of the Mayo Clinic offer a possible alternative explanation for anticipation These workers have proposed that if anticipation were indeed a genetic fact it

TABLE 7 IV

Age in years at appearance of diabetes in successive generations

Juvenile Diabetic	Maternal				Paternal				Child
	Great grand mother	Grand mother	Grand father	Mother	Great grand father	Grand mother	Grand father	Father	Age at Onset (yrs)
A C				32			56		11
T C						54		23½	1
T C						54		23½	1 3
K D	58	50							3 2
M F	Yes	49							1 2
W R					Yes		65		12
T D							38		4
B D		51							7 5
W B			51						11 3
L C						50			11 7
E H		50							7
M H							79		7 8
N J			50						5
J J		65							6 1
R K						42			8 8
W K			57						4
C Z									2 5
E M		70				63			14 7
M M			48						8 5
D M		62							6 1
B M						62			10 5
R G						65			8
G S						35			4
E R		51							6
D S							67		13 1
P S						69			6 1
D M		70							10 6
R L		Yes							11 7
G S							44		4 5
W S						Yes			5 2
C S			49						8 5
B S			49						1 8

should manifest itself in an earlier onset in the offspring irrespective of the age of onset in the parent This is not so until the age group beyond 60 is reached They therefore conclude that so called anticipation is a statistical fact based on nonrepresentative sampling This arises from the following a) prior to the discovery of insulin all juvenile diabetics died, leaving a larger proportion of older diabetics to bear children b) those women who did reach childbearing age had fewer successful pregnancies therefore it is those who developed diabetes after the childbearing age that have children with diabetes and c) the more seriously ill patients tend to seek the attention of clinics and physicians and these are usually the patients in whom diabetes has had an earlier onset The report of Thompson Laakso and Watson is consistent with this interpretation (12h) Our own limited experience is shown in Table 7 IV

C Diabetes in Twins Sex linked Diabetes

John (13a) in 1934 summarized the published reports of diabetes occurring in 19 sets of twins In three sets the onset appeared to be simultaneous in three other pairs the interval between the clinical recognition of the disorder was several weeks in the remainder the ages of onset differed by 1 to 48 years

In a 1939 summary of Berg s data (13b) a total of 411 pairs of twins one or both of whom were diabetic wa reported in a series of 85 000 diabetics and 147 pairs were studied On these 46 were classified as monozygotic and 87 as dizygotic It was found that after the age of 43 all identical twins were concordant *i e* developed diabetes Hence it is possible that the discordant monozygotic twins reported by Warkany Guest, and Cochrane (13c) one of whom developed diabetes at age 6 while the other re*mained nondiabetic though obese will become concordant at a later age*

There has been one report of so called sex linked diabetes in a family with 6 children in which only the 3 boys became diabetic (13d)

Another interesting association is that of diabetes in twin girls and an inability to taste phenylthiocarbamide (case of Segall cited by Hovanitz (13e))

Summary

Juvenile diabetics make up some five per cent of the total diabetic population of this country but compared to adults present problems out of proportion to their small numbers Other differences between the juvenile and adult forms of diabetes include the equal sex ratio the greater frequency of symptoms the shorter interval between onset and diagnosis and the higher incidence of diabetes in the families of juvenile diabetics The concept of anticipation *i e* the earlier appearance of diabetes in successive generations is attractive but disputed

One or more of the common symptoms (polyuria, polydipsia, weight loss, fatigability, polyphagia) is present in more than 90 per cent of the juvenile diabetics, but the average interval between the onset of these and other symptoms and the diagnosis is almost three months Approximately half of the diabetics are diagnosed within 30 days and in some 20 per cent the diagnosis is first made during admission in acidosis or coma

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were about 10 mg per cent higher than those in venous blood obtained virtually simultaneously, with a range of 0 to 20 mg per cent In some clinics samples of serum separated from venous blood are analyzed for sugar content The values in serum exceed those in oxalated venous blood by about five per cent because of the lower water content of blood cells (1e)

C Fasting Blood Sugar Values in Untreated Juvenile Diabetics

The blood sugar levels in untreated newly-discovered glycosuric children ultimately proved to have diabetes are shown in figure 8 3 (11) It is evident that in about 85 per cent of the children the concentration of sugar in venous blood during the fasting state clearly exceeds the upper limit observed in their nondiabetic confreres under the same conditions In those in whom the elevation is equivocal or inconsistent, measurement of the blood sugar responses to a test load of carbohydrate should be determined

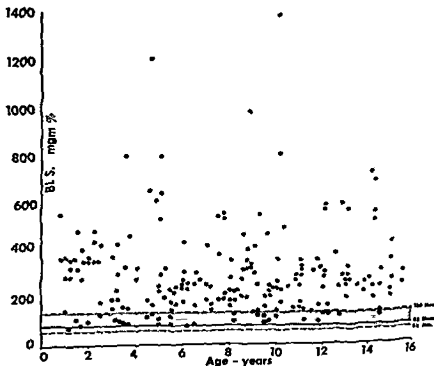


FIG 8-3 FASTING VENOUS BLOOD SUGAR LEVELS IN NEWLY DISCOVERED UNTREATED DIABETIC CHILDREN

In approximately 85 per cent of the newly-discovered diabetics in our series the blood sugar levels were above the highest values seen in *healthy nondiabetic children* The shaded portion represents the controls (1 l)

II The Use of Glucose Tolerance Tests in the Diagnosis of Diabetes General Considerations

A Factors Which Influence the Rate of Disappearance of Administered Glucose

It must be remembered that glucose tolerance tests do not reflect utilization solely They are best thought of as an indication of the rate at which glucose disappears from the circulation and from the extracellular fluid as a whole It is obvious that in addition to any utilization of carbohydrate which may be taking place segregation of glucose in tissues such as the kidney excretion in urine deposition as liver or tissue glycogen and new formation of glucose from carbohydrate and noncarbohydrate precursors will simultaneously influence the rate at which the blood sugar level changes

B The Importance of Standard Basal Conditions

The interpretation of the results of tolerance tests necessitates adequate control observations obtained in suitable subjects under comparable conditions of diet physical activity emotional stability etc Observations made beyond the two hour point must take into account the hypoglycemic tail which follows carbohydrate administration (1m–o)

1 **Effect of Senescence** Due allowances must be made for the decrease in carbohydrate tolerance which usually appears with aging in adults since it takes longer for the blood sugar to return to normal (2a h) This is not a function of absorption since it is equally evident following the intravenous administration of glucose (2g)

2 **Carbohydrate and Electrolyte Content of the Diet** Recognition of the fact that *carbohydrate deprivation or starvation impairs carbohydrate* tolerance and may actually produce starvation diabetes (2i j 3a i) necessitates an adequate provision of food intake for several days prior to a glucose tolerance test The usual recommendation has been 300 gm of dietary carbohydrate per day (3j) though amounts as low as 100 gm may be adequate for most individuals (3k)

The electrolyte content of the diet may also be important since on a high sodium intake the tolerance for glucose increases while sodium restriction produces a decrease (3l) changes which may be mediated through alterations in the level of adrenocortical activity induced by such regimens (3m–o)

3 **Effect of Physical Activity** The degree of physical activity must be taken into account in interpreting test results since bed rest by itself decreases glucose tolerance (4) Conversely the accelerating effect of exertion

upon the disposal of carbohydrate loads should be eliminated during tolerance procedures

4 Miscellaneous Factors Which May Affect Tolerance Procedures The effect of emotional disturbances on blood sugar levels is well recognized and hence undue trauma and emotional turmoil should be minimized Some thought should be given also to the possible effects of antecedent glucose or insulin tolerance procedures or anesthesia and surgery since they may alter the response (5a–d) Finally care must be taken to characterize the patient as completely as possible Disease states such as cirrhosis muscular dystrophy, peptic ulcer, *nervous system disorders* enteritis asthma and sprue endocrine factors such as anterior pituitary disorders thyroid dysfunction and adrenocortical disturbances and therapeutic agents such as epinephrine desiccated thyroid and adrenocortical steroids are some of the factors known to modify blood sugar responses to glucose administration (5e–j) With the exception of sprue these variables are discussed in other chapters

It must be admitted however that even with careful attention to all known factors the results of tolerance procedures cannot be duplicated exactly nor do they show a predictable trend in serial studies (5k)

III Experiences with Glucose Tolerance Tests in Other Clinics

Suggestions as to the optimal dosages of carbohydrate the mode of administration and the most informative schedules and routes of blood sampling in the use of oral or intravenous glucose tolerance tests have been made by many workers Three general types of tests have been employed to compare the responses in nondiabetic and diabetic subjects the single dose oral test the divided dose oral or Exton Rose procedure and the intravenous glucose tolerance test

A The Single Dose Oral Glucose Tolerance Test

The so called standard oral test in use for the past 40 years has consisted of the ingestion of 100 gm of glucose or 1 75 gm per kg of body weight dissolved in several ounces of water and flavored with lemon juice if desired The earlier workers showed that with this dosage the one half hour peak is approximately 170 or 180 mg per cent in the nondiabetic and *concurrent glycosuria is virtually nil* (6a–c) In diabetics the one half hour level is usually elevated above 200 mg per cent though usually the failure of the blood sugar concentration to return to normal or below at two hours rather than the one half hour recorded peak is used for diagnostic purposes (6d–l)

The knowledge (6m) that the dog can utilize approximately 1 0 gm of glucose per kg of body weight per hour makes the 100 gm or 1 75 gm per

kg of body weight dosage schedule a reasonable one for adults but the former provides an unduly large dosage in small children and the latter does the same in obesity Only a few workers have reported on the use of oral glucose tolerance tests in children Most of these are based on the 1 75 gm per kg dose from the age of three on Larger amounts are used for younger children 2 5 gm per kg in the age group 0 to 1½ and 2 0 gm in those who are 1½ to 3 years old The problem of glucose tolerance tests in obesity is discussed in section VI of this chapter

B The Exton Rose Test

In 1934 Exton and Rose (7a) set up standards for the response of the nondiabetic and diabetic adult to 100 gm of glucose taken by mouth in divided dosage *i e* 50 gm at zero time and 50 gm 30 minutes later According to their criteria for the nondiabetic the increment in blood sugar concentration at 30 minutes *i e* prior to the second dose of glucose should be 75 mg per cent or less at 60 minutes following the start of the test the blood sugar should be either lower the same or no more than 5 mg per cent higher than at the 30 minute point In the diabetic the blood sugar at 60 minutes is at least 10 mg per cent higher than at the 30 minute observation and usually exceeds 180 mg per cent

1 The Sensitivity and the Validity of the Exton Rose Procedure A number of workers early indicated that the test yielded an unduly large number of false positives and proposed modified standards to eliminate these (7b–g) Subsequently however Langner *et al* (7h) criticized the postulate that the first administration of glucose in the Exton Rose procedure served as a priming dose which then permitted the body to dispose of a second dose more rapidly (the so called Hamman Hirschman effect Staub Traugott phenomenon or Allen s paradox (5a 7i–k)) They pointed out that the absorption of glucose from the gastrointestinal tract did not occur rapidly enough and that the Exton Rose and the 100 gm single dose procedures are essentially the same The finding by Leonards and Free (7l) that at the end of 1 hour over one half of the glucose administered in the Exton Rose test could be aspirated from the stomach supports this objection Nevertheless the test has been used to date with various modifications in adults and in children (7m s) and the results obtained have been compared with those compiled with the single dose oral test by Moyer and Womack (7o s) These workers found that the criteria set up by Matthews *et al* (7d) applied to their data still proved too sensitive Goldberg and Luft however are of the opinion that the two dose oral test gives results that are less variable than those obtained with the single dose oral or the intravenous procedures (7t)

Recently Goto (7u) has pointed out that the Hamman Hirschman or

Staub effect referred to above may or may not be elicited in a nondiabetic, depending upon the timing of the second dosage of glucose He suggests that the effect is artefactual and depends on the superimposition of a second normal tolerance curve on the hypoglycemic "tail" of the first If these observations are valid it is obvious that in the Exton-Rose test this cannot be a factor, since there is no hypoglycemia at the 30 minute point

C The Intravenous Glucose Tolerance Test

Blumenthal's (8a) and Thannhauser and Pfitzer's demonstrations (8b) in 1905 and 1913 that blood sugar levels could be raised in humans by the intravenous administration of glucose were probably the first intravenous glucose tolerance tests Shortly thereafter Woodyatt *et al* (8c) in this country reported details of their studies on prolonged and accurately timed intravenous injections of sugars (8b–d)

1. The Variety of Intravenous Glucose Tolerance Tests. The tolerance procedures which have been employed have differed in the total dosage of glucose, the concentration of the infused solution, and the duration of the infusion (7o–s, 8e–g) In such studies the total amount of administered glucose has varied from a single fixed dosage of 25 gm to a schedule of 0 5 to 0 8 gm per kg of body weight The concentration of the solution has ranged from 20 to 50 per cent in distilled water The concentrated solutions are injected in several minutes The more dilute solutions have been given during 10 to 30 minutes In studies in children Ross (8e) has employed a dosage of 0 5 gm per kg of body weight given promptly The findings of Ross (8e) and those of Lozner *et al* (8g) indicate that at 5 minutes the maximum blood sugar levels achieved are in excess of 300 mg per cent and hence glycosuria can be expected to occur Actual measurements indicate this glycosuria to be limited to 2 5 gm or less (8h)

2. The Use of Intravenous Glucose Tolerance Tests in the Diagnosis of Diabetes. It is obvious that the variety of dosage schedules employed does not permit detailed comparison of one intravenous glucose tolerance test with any other, but in general the diagnosis of diabetes mellitus is based upon the presence of an elevated blood sugar concentration at the 2 hour point Thus, in the Lozner series (8g) 2-hour values higher than 120 mg per cent are taken to be indicative of diabetes Those which fall in the range between 120 and 140 are inconclusive The peak at ½ hour may be useful in identifying patients with hepatic disease (see section VI of this chapter), but generally is not considered to be of assistance in the diagnosis of diabetes mellitus

Moyer and Womack (7o–s) believe that in detecting diabetes the intravenous test which they use (0 5 gm per kg given during a 20 minute period) is less effective than the standard 100-gm oral glucose tolerance

test The work of Scow and Cornfield (81) demonstrating that the removal rate for glucose given *per os* is three times as high as that given intravenously may have some bearing on this point it may be as they suggest that the hepatic disposal of glucose is influenced by the mode of administration Also the lower sensitivity may account for the greater reproducibility of intravenous tolerance tests in animals (83)

IV Detailed Results of Responses to Oral or Intravenous Glucose Tolerances in Diabetic and Nondiabetic Children Pittsburgh Series

Despite the large body of published information on glucose tolerance tests there is no detailed study of the blood sugar and electrolyte changes which occur in diabetic and in healthy nondiabetic children during the various types of tolerances under comparable conditions We have therefore compiled our own control data[1] for the interpretation of results in children suspected or known to have diabetes To produce the sharpest separation of the diabetic and nondiabetic groups we have administered glucose *per os* or intravenously in the larger or largest dosage in ordinary usage This dosage the route of administration the time of blood sampling and the source of blood were clearly noted in each instance since they are always of prime importance in the interpretation of any test result This information can be used by others as a valid standard of reference provided that the control and test situations are identical and the analytic procedures yield comparable results

A Single Dose Oral Glucose Tolerance Test

The dosage of glucose in the single dose oral glucose tolerance tests was 1 75 gm per kg of body weight given at zero time dissolved in one or more glasses of water flavored with lemon juice Fingertip capillary blood was obtained prior to and at 30 60 120 and some at 180 minutes (1- to 2 minute leeway) following ingestion of the glucose

1 Results in Healthy Nondiabetic Children From figures 8 4A and 8 4B it is evident that in these nondiabetic children the fasting levels in capillary blood averaged 100 7 ± 9 0 mg per cent The observed peak in blood sugar concentration was recorded at 30 minutes in 27 of the 30 tests in the remaining three a further rise was observed at the 1 hour point It is to be noted that at two hours the blood sugar values were the same as or just slightly higher than the fasting levels At 180 minutes the concentrations dropped below the mean fasting levels All of these differences are statistically significant

[1] The control data are based on studies conducted in a privately supported well run home for children with a stable population Tolerances were determined in the fasting state at bed rest with minimal trauma

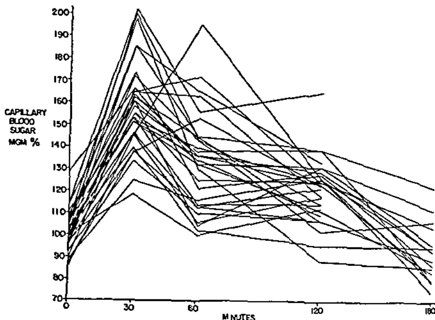


FIG 8-4A CHANGES IN CAPILLARY BLOOD SUGAR FOLLOWING THE ORAL ADMINISTRATION OF A STANDARD AMOUNT OF GLUCOSE

These 30 healthy nondiabetic children received glucose 1 75 gm per kg of body weight at zero time dissolved in approximately 100 ml of water flavored with ½ tsp of fresh lemon juice The maximum and minimum values recorded at 30 min were 202 and 119 mg per cent respectively At the 60 min point the levels were still increased above the preinjection concentrations in almost all of the subjects though decreases were apparent in all but three of the children It is to be noted that the range at 2 hours extended from 89 to 168 mg per cent and that a hypoglycemic trend or tail is evident at 3 hours in some of the curves (1 1)

In employing these control data for clinical purposes either the individual or the pooled experiences may be used Thus in the former (figure 8 4A), *none of the subjects had a 30 minute blood sugar level greater than 202 mg* per cent and some showed a subsequent slight rise at 1 hour but the majority decreased The two hour point might indicate a slight decrease a slight rise or no change upon comparison with the 1 hour point At this time 29 of the 30 sugars were at or below 140 mg per cent At 3 hours most of the curves had reached or dropped below the fasting concentrations with a range of 79 to 123 mg per cent If the composite curve (figure 8 4B) is used as a reference *it should be remembered that one* standard deviation (S D) encompasses 66 6 per cent of the points that two S D include 95 per cent and three S D cover 99 per cent of the distribution Hence, any observed point less than two S D away from the mean

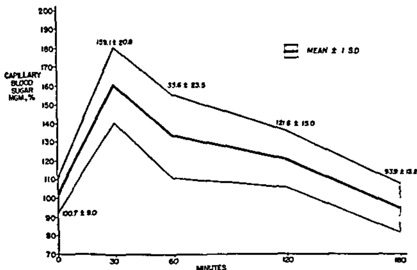


Fig 8-4B Single Dose Oral Glucose Tolerance Test Results Expressed as Mean Values

The individual curves of figure 8-4A are shown as mean values ±1 S.D

Oral GTT

BL. S. mgm. %

Minutes

Fig 8-5 Oral Glucose Tolerance Tests (1.75 Gm per Kg) in Diabetic Children

Measurements of levels in capillary blood are shown by dotted lines and in venous blood by solid lines *The shaded area represents the responses (mean ±1 S.D) of nondiabetic children to the same dosage of glucose as in the preceding figure (11)*

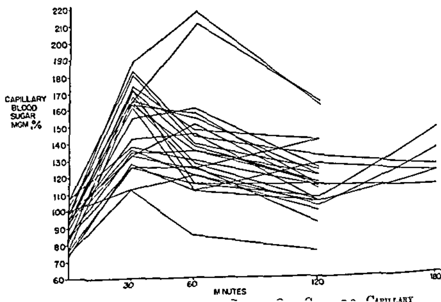
is within the normal range Values clearly more than three S D away from the mean are probably abnormal

2. Results of Single Dose Oral Glucose Tolerance Tests in Newly-Discovered or Previously Diagnosed Diabetic Children. In this group of 17 diabetics the fasting levels of blood sugar were elevated above the normal range in all but two patients One-half hour following the oral intake of glucose the blood sugar increased by 91 to 203 mg per cent with a mean increment of 120 mg per cent (figure 8-5) This is to be compared with the lesser rise noted at this time in the nondiabetic controls Furthermore the subsequent measurements at 1, 1½, or 2 hours following the ingestion of glucose a further increase was usually noted with only an occasional slight decrease (figure 8-5)

It is obvious in retrospect that the same conclusion concerning impairment of glucose disposal would have been reached in each of these patients had the test been terminated at 1 hour.

B Doubled Dose Oral Glucose Tolerance Test

In keeping with the general goal of setting up standards based on a heavy carbohydrate load we have administered glucose in this test in a



Capillary
75 gm of
gle dosage
(1 1)

studies in similar subjects (fig 8-4) ...

total dosage of 3 50 gm per kg of body weight One-half of this, or 1 75 gm per kg, was given at zero time and the remainder 30 minutes later Capillary blood sugar levels were measured at 0, 30, 60, 90, 120, and 180 minutes It is to be noted that this is not a single oral dose divided into portions as is true of the Exton Rose procedure, but a doubled dose designed to intensify the difference between the diabetic and nondiabetic It is administered in divided amounts because the ingestion of the total at one time may produce nausea and vomiting

1. Findings in Healthy Children. The results, individual and composite, are presented in figures 8 6A and 8 6B, respectively The findings at the 30 minute point prior to the second dose of glucose, are of course quite comparable to those seen at the same time in the single dose test The mean values in figures 8-6A and 8 6B based on the 1 75 gm dosage are indistinguishable and the range is of the same order of magnitude It is to be noted that the second dose of glucose as a rule did not raise the 60-minute sugar levels above those present at the ½ hour point The course of the blood sugars upward, downward or without change as well as the

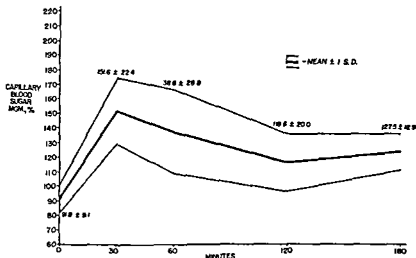


Fig 8-6B Responses of Healthy Children to Oral Glucose in Doubled Dosage Mean Values

Studies and patients are the same as those shown in the preceding figure The similarity to the average response to 1 75 gm per kg (see fig 8-4B) is to be noted This is present in healthy children despite the fact that the initial ingestion of glucose at zero time was repeated at 30 min The 180-min response is based on too few observations to warrant a generalization (1 1)

mean value is quite reminiscent of the trends in the single dose tolerance tests

At 120 minutes the mean blood sugar levels in the doubled dose test are the same as those observed in control subjects after 1 75 gm per kg At the end of 3 hours, however, the blood sugar in the 3 50 gm per kg test is distinctly above that in which only one-half of this amount of sugar was given, *i e*, absorption continues for a longer period of time

2. Blood Sugar Findings in Diabetic Children Prior to and Following the Oral Administration of a Total of 3.50 Gm. of Glucose per Kilogram of Body Weight in Divided Dosage at Zero and at 30 Minutes. Again, as in the single oral dose studies, the blood sugar levels prior to glucose administration were not always clearly elevated above the normal range At the 30 minute point the initial 1 75 gm per kg dosage of glucose had produced an increment in the blood sugar which was greater than that observed in the controls, ranging up to 385 mg per

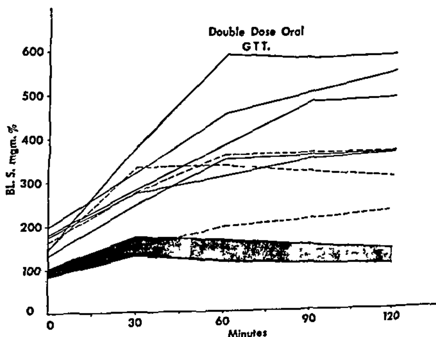


FIG 8-7 DOUBLED DOSE ORAL GLUCOSE TOLERANCE TESTS IN DIABETIC CHILDREN The shaded area represents the capillary blood sugar responses (mean ±1 S.D) of nondiabetic children to the same dosage of glucose as in the preceding figure The non diabetic and diabetic children each received *1 75 gm of glucose per kg of body weight per os* at zero time and again at 30 min Dotted lines identify capillary blood sugar curves, solid lines refer to venous blood (1 I)

cent (figure 8 7) Following the second dose of glucose most of the diabetic children showed a progressive rise at 60 and 90 and even 120 minutes in contrast to the return to the fasting levels observed in the nondiabetic children However, the 60 minute level is by itself frequently diagnostic of impaired carbohydrate tolerance

C Intravenous Glucose Tolerance Test in Healthy Children

Responses to an injection of 50 per cent glucose in water, 0 5 gm of carbohydrate per kilogram of body weight, have been determined following infusion of the sugar during a 3- to 5 minute period

1. Results in Control Studies Preinjection blood sugar concentrations were all within the normal range established for nondiabetic children (figure 8 8A and 8 8B) The mean 30 minute blood glucose concentration was 145 4 ± 25 4 mg per cent If the isolated instance is excluded it will be seen that in 26 of the 27 tests the ½ hour value was between 110 and 185

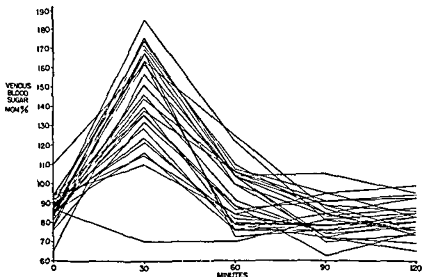


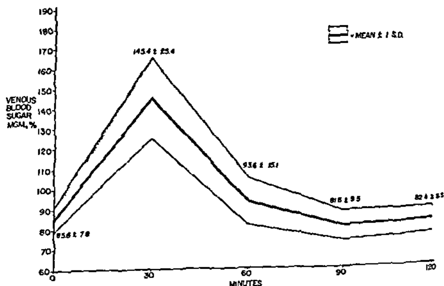
FIG 8-8A THE VENOUS BLOOD SUGAR CHANGES FOLLOWING INTRAVENOUS GLUCOSE INDIVIDUAL CURVES

Subjects are healthy nondiabetic children at bed rest throughout the tolerance test The rapid infusion of 0.5 gm of glucose per kg of body weight during 3 to 5

mg per cent Although a considerable return toward normal was recorded at the end of one hour the mean of these points is still above the starting values At 90 and 120 minutes, however, the levels were again the same as those present prior to the administration of the carbohydrate

2. The Response of Diabetic Children to Intravenous Glucose The introduction of 0 5 gm of glucose per kilogram of body weight in these diabetic children resulted in a 30 minute increment which was usually no *higher than that observed in the nondiabetic* The absolute concentrations were usually greater because of the higher fasting blood sugar levels In virtually all cases the 60-, 90 , and 120 minute levels were higher than in the nondiabetics (*figure 8 9*) and here for diagnostic purposes the 1 hour level could have been used as effectively as the 2 hour level

It is to be observed that with the oral procedures which provided much larger glucose loads the diabetics continued to show either a progressive increase in blood sugar levels or only a very slight decrease during the course of the 2 or 3 hours of observation This means of course that in the oral tests the diabetic continues to absorb glucose at a rate in excess of his capacity to dispose of it and that this accumulated glucose produces progressively higher levels of blood sugar *With the smaller single intra*



ance
lood

venous injection at zero time without a further glucose load a decrease was invariably recorded

V Can the Glucose Tolerance Test Be Shortened to 1 Hour?

It is obvious from the data on control and on diabetic children that the diagnosis of impaired carbohydrate tolerance could have been made *with out a single exception* from the 1 hour glucose concentration in these series The subsequent points serve to differentiate abnormal peaking as a result of increased absorption as in hyperthyroidism or decreased disposal by glycogenation as in liver disease from true diabetes mellitus It may well be that the later points also eliminate false negative tests resulting from delayed gastric emptying time Also it is obvious that the diagnosis is much more definite with the progressive and marked rises recorded in the 1 75 and 3 50 gram per kilogram oral tolerances Finally the hypoglycemic

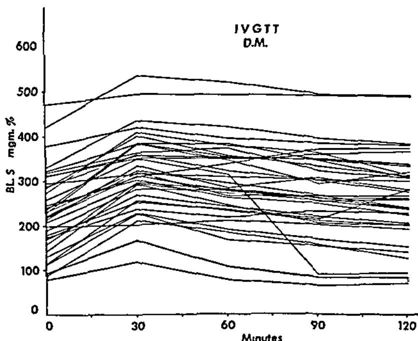


Fig 8 9 Results of Intravenous Glucose Tolerance Tests in Diabetic Children

5 gm per kg

epresents the

to the same

tail present at two hours and listed as characteristic of tests in nondiabetics is not available as an additional index if the sampling is limited to one hour For these various reasons we have continued with the 2 hour procedures although if one were dealing solely with uncomplicated diabetes and the results of analysis were uniformly reliable the 1 hour test would suffice Observations at time intervals of one minute have been used in sucrose tolerance tests (8k) but none has been reported following glucose Attempts to produce a sharper differentiation between diabetics and nondiabetics have been made using cortisone or indices other than the blood sugar levels i e disappearance rate total index increment index etc (8l w)

VI Effects of Obesity, Hyperthyroidism, Absorption Defects or Cirrhosis on Glucose Tolerance Procedures

A In Obesity

The problem of carbohydrate dosage in tolerance procedures carried out in obese patients is both real and unsolved (9a–d) If the actual body weight is used the patient receives more than the usual dosage per kilogram of active protoplasm estimation of the ideal body weight for a particular patient *i e* if he were not obese and basing the carbohydrate dosage on that provides at best an approximation Furthermore in view of the larger surface area and the greater need for heat production in obesity it is obvious that simple extrapolation to a lean body mass does not correct for these factors For these reasons it is our practice to consider the question of dosage in glucose tolerance procedures in obese patients an open one We [illegible] on the actual

ve con

unim

paired If only the first is abnormal the patient is continued under observation as a *potential or actual diabetic It is of interest* that abnormal tolerance tests compatible with the diagnosis of diabetes may return to normal with successful weight reduction (9e–j)

B In Patients With Absorption Defects

In patients who have steatorrhea or sprue or other absorptive limitations (*10a b*) *carbohydrate metabolism can be more accurately* evaluated by means of the intravenous tolerance test This bypasses the absorption defect and at the same time permits identification of enhanced disposal as a possible factor in a so called flat *glucose tolerance response* On the other hand it has been noted that cancer of the pancreas may result in an impairment of glucose tolerance of the diabetic type and conversely that cancer of the pancreas is more prevalent amongst known diabetics (*10c–f*)

C In Hyperthyroidism

In hyperthyroidism one might expect the ½ hour peak to be unduly high in oral tolerance procedures because of the enhanced absorption of glucose Furthermore on the grounds of the known effects of thyroxin excesses (increased gluconeogenesis and liver deglycogenation which might overweigh the enhanced peripheral disposal) altered carbohydrate tolerance might well be anticipated In actuality results of glucose tolerance tests are grossly normal except in those patients who have diabetes (11a, b), though minor deviations have been detected

D In Cirrhosis

Patients with cirrhosis and evidences of decompensated liver function show an unusually high level of blood sugar 30 minutes following the oral or intravenous administration of glucose (7o 12a-p) In most patients the subsequent values decline to levels approximating those observed in non cirrhotic control subjects As a group however these values are somewhat higher and in this laboratory and elsewhere this difference has been shown to be statistically significant (see Chapter 9 section V) In practical terms however this should not lead to confusion with diabetes in which the differences are much more pronounced

E In Combination With 11-Oxysteroids

Fajans and Conn have been testing the effect of cortisone administration as an aid to the early diagnosis of diabetes mellitus (13) In a group of 323 relatives of known diabetics a 20 per cent incidence of unsuspected diabetes was found whereas in a control group of 100 nondiabetics abnormal glucose tolerance tests were encountered in only three

Summary

In approximately three quarters of untreated newly discovered juvenile diabetics the blood sugar is elevated above the range of values observed in the fasting state in healthy children of the same age Such hyperglycemia is therefore highly suggestive of the presence of diabetes, provided that food intake has been normal and ingestion or administration of car-

betes must still be excluded

In those patients in whom unequivocal fasting hyperglycemia is absent, the diagnosis of diabetes depends upon a demonstration that an inability to dispose of carbohydrate loads at normal rates and without undue hyper-

glycemia is present This can be tested by obtaining a measurement of the blood sugar level two hours following upon an ordinary meal but is usually determined more precisely by means of a glucose tolerance test Of the various procedures available the oral administration of a fixed or a per kilogram dosage of glucose is most commonly employed In the adult 100 gm of glucose are usually given, in children older than 3 years of age the amount of glucose is determined by body size *i e* 1 75 gm are given per kilogram of body weight Alternatively, intravenous glucose, 0 5 gm per kilogram of body weight as a 50 per cent solution in water, or a fixed dosage of 25 gram in adults may be administered It may be however that these lesser amounts given intravenously are less sensitive in detecting the presence of diabetes even though they by pass variations attributable to accelerated or delayed absorption The Exton Rose procedure in which the same amount of glucose administered in the single dose oral test is given in two equally divided portions 30 minutes apart is based on an unwarranted assumption We have found satisfactory however a doubled dosage tolerance test as a means of administering as large a glucose load as possible without producing vomiting In any of these procedures the two hour or three hour blood sugar level is more informative than the peak which is usually recorded at 30 minutes In any tolerance procedure suitable reference standards taking into account the dosages employed and the age of the patient must be used The simultaneous measurement of urine sugars may help detect undue hyperglycemia present between the arbitrarily selected sampling times but this is not usually necessary Finally the diabetic response has to be differentiated from the increased 30 minute peak and somewhat retarded delay in the return of the blood sugar to preinjection levels which characterize the cirrhotic

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CHAPTER 9

Serum Electrolyte Changes Following the Administration of Glucose

There have been a number of attempts to simplify or to make more accurate the identification of diabetes by measurement of the serum electrolyte changes which accompany the disposal of glucose. The rationale of such searches is based on the knowledge that glycolysis and glycogen deposition are preceded by phosphorylation (1a–t) and removal of serum inorganic phosphorus and that potassium enters cells in conjunction with the degradation of glucose and the deposition of glycogen.

I. Changes in Inorganic Phosphorus Following the Administration of Glucose to Animals and to Nondiabetic and Diabetic Human Adults

A. Relationship of the Change in Serum Inorganic Phosphorus to the Presence or Absence of Diabetes and Other Factors

In 1923 Perlzweig, Latham, and Keefer (1a) reported that in the nondiabetic human the administration of 50 or 100 gm. of glucose definitely lowered the serum levels of inorganic phosphorus and diminished the urinary excretion of phosphate; this did not occur in the diabetic patient not on insulin. Subsequent observers have established the fact that this change in serum inorganic phosphorus is an invariable occurrence in the intact animal and in the nondiabetic and, though perhaps of lesser degree, in the diabetic human receiving carbohydrate *per os* or via the intravenous route (1b–n).

1. Studies Pointing to a Quantitative Difference in the Responses in Diabetics and Nondiabetics. In most of the subsequent studies a difference between the responses in diabetic and nondiabetic humans was reported to be present, though the separation of the two groups was not as pronounced as Perlzweig *et al.* (1a) indicated. Thus, Hartman and Bolliger (1c, d) felt that the responses were sufficiently distinctive to classify the responses as normal or abnormal and drew inferences concerning the function of the pancreas and other endocrines. McCullagh and Van Alstine (1f) agreed that abnormalities of serum inorganic phosphorus changes following glucose were frequent in endocrine disorders, and occurred in one-half of their diabetics, but stated that they were not sufficiently distinctive for differential diagnosis. On the other hand, DeVecchi (1j),

working with diabetics, used the $\Delta G/\Delta P$ ratio i e, the rise in blood sugar level 30 minutes following the ingestion of glucose in relationship to the simultaneous decrease in serum inorganic phosphorus and concluded that a positive ratio indicated defective insulin production Similarly Forsham and Thorn (1k) employing a ½ hour infusion of a 20 per cent solution of glucose in water for a total dosage of 0 5 gm per kg of body weight, found that in control subjects the serum inorganic phosphorus decreased by 25 per cent at the 60 or 90 minute point following the start of the infusion in diabetic subjects the decrease was less averaging 12 per cent, in patients with cirrhosis it was greater with a mean of 37 per cent Furthermore, in both the diabetic and the cirrhotic patients the fall was prolonged compared to the normal

2. Reports Indicating Similarity or Identity of Phosphorus Changes in Diabetics and Nondiabetics On the other hand some workers have felt that either there are no differences in the serum phosphorus responses of the diabetic and nondiabetic or that if present they are slight and the overlap of the two groups is too great to allow use of a lesser phosphorus decrement as an identifying characteristic of decreased carbohydrate metabolism Kret (1l) has even concluded from the results of prolonged infusion of glucose in large amounts that the direct effect of such extra carbohydrate is a delayed increase in serum inorganic phosphorus and that the early decrease is an indirect result mediated through insulin Groen *et al* (1m) who gave glucose by mouth or by vein for a total of 100 to 150 gm found that the phosphorus decreased and returned to normal in the course of 6 to 9 hours but failed to observe the rise described by Kret (1l) They found that the pattern was the same in a patient with hepatic necrosis but absent in another with muscular atrophy their series did not include diabetics Schneeberg (1n) in evaluating the phosphorus responses in mild and moderately severe diabetics compared to normals on the basis of either the absolute changes or the $\Delta G/\Delta P$ ratio concluded that the scatter of values precluded their use as an index of diabetes despite the fact that the differences between the mean values for the two groups were statistically significant Runyan and Kantor (1o) gave 100 gm of glucose to 37 mild diabetics and 20 control subjects and observed no differences in the phosphorus changes in the two groups Lazarus Volk *et al* (1p) have suggested that the diabetics who have a normal phosphorus decrease accompanied by a decrease in circulating lymphocytes have a nonendocrine diabetes on the basis of hepatic dysfunction

B Mechanism of the Decrease in Serum Inorganic Phosphorus Following Carbohydrate

The mechanism of the change in serum inorganic phosphorus can be inferred from available studies The decrease cannot be attributed to losses

As in the case of phosphorus the presence of liver necrosis had no effect on the potassium change whereas it was not observed to occur in a patient with extensive muscular atrophy They made no comparisons with diabetics Wilson and Thorn (3a), using the 0 5 gm per kg dosage of glucose given as a 20 per cent solution during ½ hour, found that there were no definite differences between the potassium responses of the diabetic and nondiabetic subjects In the studies of Runyan and Kantor referred to earlier (1o) the change in serum potassium was the same in diabetics and nondiabetics, averaging −0 32 and −0 33 mEq per liter, respectively These were based on analyses of venous blood It may well be that changes in arterial, i e, capillary, blood might have shown a difference in these and in the other short-term studies cited, since Farber *et al* (3b) have shown that in the fasting state venous and arterial potassium levels are the same, but that this is no longer true following glucose or insulin administration

B Possible Explanations for the Similarity of Responses in Diabetics and Nondiabetics

In many ways this lack of a definite difference in the serum potassium responses of diabetics and nondiabetics following glucose administration is rather surprising In the isolated blood cell system (4a–e) and in brain slices (4f) the disappearance of glucose via glycolysis removes potassium from the serum or the surrounding medium Furthermore, the deposition of glycogen has long been known to pre-empt extracellular potassium (1s, 4g, h) Since these are the two chief pathways of glucose disposal in the nondiabetic animal and human, one might expect serum potassium to decrease with carbohydrate loading The fact that this does not happen means, of course, that simultaneous transfers of water out of the extracellular space or of potassium into it cancel the deficits created by glycolysis *and glycogenation The effect of glucose on the osmotic pressure* difference (2a) would appear at first sight to preclude the first of these possibilities It may be, however, that the osmotic effect of the glucose is sufficiently dehydrating to produce *the well-recognized release of cell* potassium as a part of the dehydration reaction (4i, j) In studies in which an infusion of dilute glucose solutions is given slowly enough to minimize the osmotic effect one might expect, as Groen *et al* have found (1m), a drop in the serum potassium

III. Data on Changes in Electrolytes Other Than Phosphorus and Potassium Accompanying Carbohydrate Administration

Very few observations have been reported on constituents other than phosphorus and potassium Harrop and Benedict (1b) observed no change in serum sodium or calcium following glucose administration Other than

our studies in children presented below there have been no reports on measurements of serum total CO_2 content and chloride

IV. Electrolyte Changes in Children and Juvenile Diabetics Following the Intravenous or Oral Administration of Glucose

A Serum Inorganic Phosphorus Changes in Sham Tolerances and Following Intravenous or Oral Glucose

1 In Healthy Children During bed rest while in the fasting state the serum inorganic phosphorus fluctuates about the first value with a mean trend that is negative At the end of two hours this is of sufficient magnitude and of appropriate direction to be definite The decrease averages 0 26 mg per cent and presumably represents a change consequent upon the transition from the early to the later phases of awakening This sequence is presented in figure 9 1 entitled Sham Tolerance (5 a-c)

On the other hand the administration of glucose by vein (0 5 mg per kg of body weight in 3 to 5 minutes) produces a prompt and statistically significant drop in the serum inorganic phosphorus (open columns, figure 9 2) At 30 minutes this averages 0 44 mg per cent in the intravenous tolerance tests and 0 33 mg per cent in the oral test following the first dose These decreases persist and are of comparable or greater magnitude at 1 hour and at 1½ hours

2 In Diabetic Children Without and With Insulin The findings in

B Serum Potassium in Sham Tolerances and Following Intravenous or Oral Glucose

... as in the case of phosphorus a gradual decline in the fasting level during the 2 hour observation period

2 In Juvenile Diabetics Without and With Insulin In diabetes mel

fasting state in nondiabetic children (figure 9 1) are replaced by a definite rise in the healthy child who has received glucose (figure 9 2), whereas the inadequately treated juvenile diabetic, i e one not on insulin and in whom serum total CO_2 content is lowered, shows a fall This does not occur however if ketosis or acidosis is absent or if insulin has been given

Presumably the rise in total CO_2 content in the healthy children after carbohydrate reflects an increased utilization of glucose and a decreased catabolism of fatty acids The latter results in decreased plasma ketone body levels and a rise in the total CO_2 content In the uncontrolled diabetic not on insulin the reliance upon fatty acids for energy purposes continues despite the administration of glucose The degradation of fatty acids to acetyl CoA definitely surpasses the rate at which they can be utilized by the tissues and hence excesses of beta hydroxybutyric and acetoacetic acids accumulate

D Serum Sodium and Chloride Levels in Sham Tolerances and During Either Intravenous or Oral Glucose Administration to Healthy Children and to Diabetics Without and With Insulin

There is no evidence that carbohydrate administration to the nondiabetic or diabetic child discernibly alters the minor changes in serum chloride and sodium evident during control observations (figure 9 2)

In summary therefore in children with a diabetic type of blood sugar response to test doses of intravenous or oral glucose, the accompanying serum electrolyte changes differ considerably from those seen in nondiabetic controls a) the decreases in inorganic phosphorus either do not occur or are much less pronounced b) the serum total CO content tends to decline during the course of the test in contrast to the rise seen in control studies and c) the potassium levels rise The sodium and chloride changes

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nature of these responses at present precludes their routine clinical use as a possible aid in the identification of borderline or unusual instances of juvenile diabetes

V Blood Sugar and Electrolyte Responses During Intravenous Glucose Tolerance Studies in Cirrhosis and in Muscular Dystrophy

... a follow ng a standard amount of
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ose load by deposition as hepatic glycogen This interpretation is supp-ed by the finding that the serum inorganic phosphorus decrease which -cts glycolysis is greater in the cirrhotics (figure 9 3) (2c)

i juvenile muscular dystrophy the ability to dispose of carbohydrate flected in tolerance tests is unimpaired The studies of Van Bekkum Querido (5a) suggest that the serum inorganic phosphorus changes ess in these patients presumably because muscle mass is diminished olved by the disease process Our observations (5b, c) (figure 9-4) in-e that though the serum inorganic phosphorus change is of lesser de-the difference is not statistically significant

Summary

knowledge that acceleration of glucose disposal following carbohy-loading is accompanied by removal of inorganic phosphorus and at of potassium from the plasma and extracellular fluid has suggested of such measurements as an aid in the detection of diabetes In l these indices have proved disappointing in that they have failed rate sharply the diabetics from the nondiabetics In our pediatric tion a similar overlap of serum inorganic phosphorus values is ap-when venous blood samples are analyzed though the mean responses rent In the untreated diabetic the potassium levels usually rise icose administration (perhaps by inducing a dehydration reaction lease of cell potassium) whereas in healthy children or in insulin diabetics the potassium concentration may remain unchanged, de-or increase Concomitant analyses for serum bicarbonate show a ontrol subjects and no change or a fall in diabetics Chloride and alues appear to fluctuate at random in both groups

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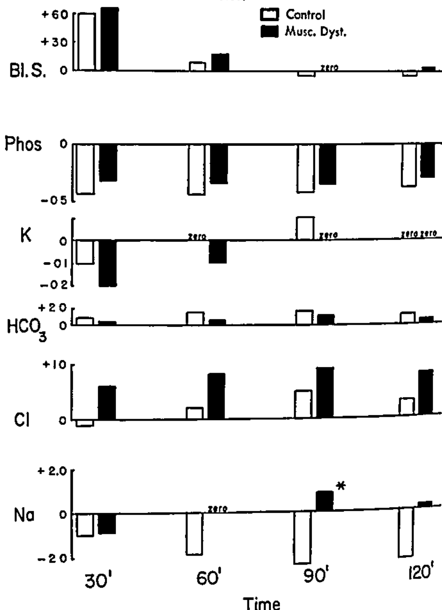


FIG 9-4 BLOOD SUGAR AND SERUM ELECTROLYTE CHANGES DURING INTRAVENOUS GLUCOSE TOLERANCE TESTS (0.5 GM PER KG) IN CHILDREN WITH MUSCULAR DYSTROPHY

... the fall in serum inorganic ... normal boys and girls (open ... solid columns) The difference in the phosphorus response in the two groups is close to statistical significance, however, in that p was 0 06 All other changes, except for the 90 min sodium, were also of the same order of magnitude in these two groups of children (5b)

glucose load by deposition as hepatic glycogen This interpretation is supported by the finding that the serum inorganic phosphorus decrease which reflects glycolysis is greater in the cirrhotics (figure 9 3) (2c)

In juvenile muscular dystrophy the ability to dispose of carbohydrate as reflected in tolerance tests is unimpaired The studies of Van Bekkum and Querido (5a) suggest that the serum inorganic phosphorus changes are less in these patients presumably because muscle mass is diminished or involved by the disease process Our observations (5b, c) (*figure 9 4*) indicate that though the serum inorganic phosphorus change is of lesser degree, the difference is not statistically significant

Summary

[illegible]

after glucose administration [illegible] with release of cell potassium) whereas in healthy children or in insulin treated diabetics the potassium concentration may remain unchanged decrease, or increase *Concomitant analyses for serum bicarbonate show a* rise in control subjects and no change or a fall in diabetics *Chloride and* sodium values appear to fluctuate at random in both groups

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phosphorus (9a–d) and of serum potassium (9c d) in addition to lowerin the level of the blood sugar These observations have been amply confirme since then (9e–n) and extended to the evaluation of variables such a mental illness vitamin deficiency hormones and ageing (9o–r)

Recent studies in our laboratory have shown that in healthy childre and young adults the intravenous administration of insulin 0 1 unit pe kg of body weight also produces a characteristic decrease in the serur total CO content and a rise in the levels of serum chloride (10a) The changes and the concomitant alterations in the blood sugar and the serur inorganic phosphorus and potassium concentrations are shown in figur 10 3 (open columns) The fluctuations in sodium show no trend

A Insulin Induced Hypophosphatemia

The mechanism of the decrease in serum inorganic phosphorus is fairl well understood The demonstration by Levine *et al* (9g h) that the ac ministration of fructose which does not require insulin for entrance int the cell and yet produces a decrease in serum inorganic phosphorus ind cates that insulin *per se* is not essential for this change This view that it the entry of glucose into the cell rather than the presence of insulin tha determines the serum inorganic phosphorus decrease is supported by th demonstration that it occurs in the totally depancreatized animal in whor a transfer of glucose into cells is produced by marked increases in the ex tracellular concentration of this sugar (9g h)

B Hypokalemia Following Insulin

The factors operative in the potassium decrease are less well define The work of Dury (11a–e) indicates that the adrenal medulla plays key role In the adrenalectomized and in the adrenal demedullated rat th potassium does not decrease following insulin administration Dury sug gests that the discharge of the adrenal medulla by the insulin induce hypoglycemia is essential for the hypokalemic response Where the pota sium goes is an unsettled question The decreases seem too pronounced t be attributable to hemodilution as a consequence of an access of cellula fluids and hence must result from transfers of potassium out of the extra cell ilar space either in urine or into cells (11f g) A number of processes ar known to produce the latter including glycolysis (12a–d) the depositio of liver glycogen (13a b) and the formation of cell protein (14)

There is as yet no explanation for the decreases in the serum total CO content and chloride increases which accompany the decreases in serur inorganic phosphorus and potassium following intravenous insulin

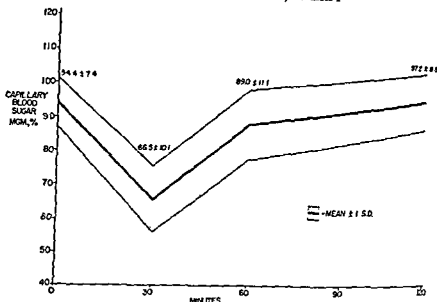


FIG 10 2 HYPOGLYCEMIC EFFECT OF INTRAVENOUS INSULIN IN HEALTHY NONDIABETIC CHILDREN

The control subjects and the studies are the same as those shown in fig 10-1 (7e) The intravenous injection of rapid-acting crystalline insulin 0 1 unit per kg of body weight (given as a freshly made 1 9 dilution in 0 9 per cent saline to assure accurate dosage) is followed by an average decrease of 27 9 mg per cent in the capillary (Hagedorn-Jensen) blood sugar levels The return to preinjection levels is virtually complete at 1 hour The figures ±7 4 ±10 1 ±11 1, and ±8.5 refer of course to the standard deviation (S.D) from the mean at 0 30 60, and 120 min, respectively

diet renders the organism less sensitive to insulin (8a, b) Recently, Guest and his colleagues (8c) have shown that acidosis also suppresses the response

Until recently the use of the insulin tolerance test in humans has been confined largely to the investigation and characterization of endocrinologic disorders other than the usual type of adult or juvenile diabetes mellitus (7b–d) Since attempts to segregate diabetes into two groups, the insulin sensitive and the insulin insensitive, have been based largely on the use of glucose-insulin tolerance tests and more recently on the results of insulin tolerance studies, these are discussed together in section V of this chapter

II. The Known Effects of Insulin Administration upon Electrolyte Concentrations in Animals and in Humans

Shortly after insulin became available it became evident that its administration produced a decrease in *the concentrations of serum inorganic*

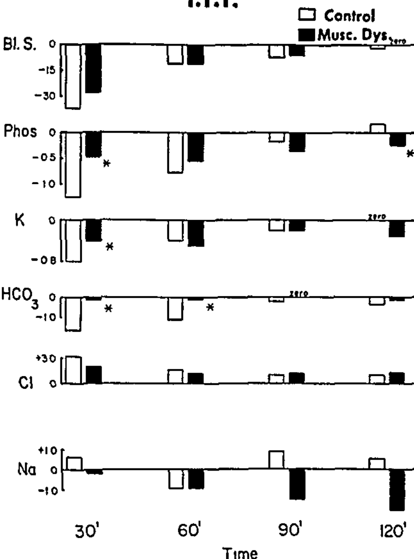


FIG 10-5 MUSCULAR DYSTROPHY AND THE RESPONSES TO INTRAVENOUS INSULIN

[illegible]

asterisked) indicate that the utilization of glucose in the peripheral tissues is decreased in children with muscular dystrophy presumably because the muscle mass is decreased or diseased (10a, b)

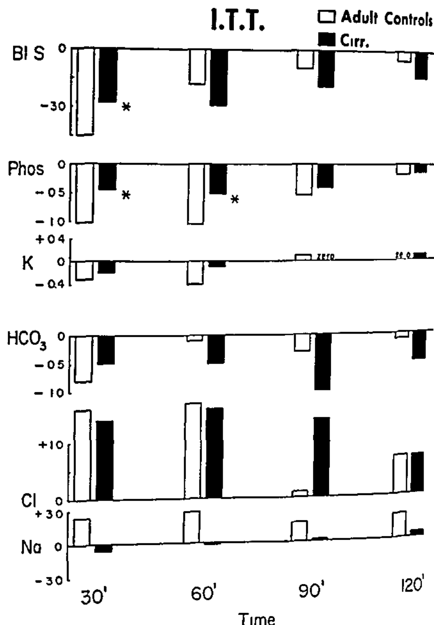


FIG 10-4 BLOOD SUGAR AND ELECTROLYTE CHANGES FOLLOWING ADMINISTRATION OF INTRAVENOUS INSULIN TO PATIENTS WITH CIRRHOSIS

Both groups of subjects were adults Each column represents the average of to 11 studies Asterisks identify differences in the responses that are statistical significant The patients with cirrhosis showed less of a decrease in the 30-m blood sugar and the 30 and 60 min serum inorganic phosphorus level following th ... (0 1 unit per kg of body weight) The pho ... f peripheral utilization of glucose i e insuli ... cirrhosis This accounts for the less pronounce

Lawrence (17m) has suggested a classification of diabetes which takes in the concept of insulin resistance In his classification diabetics fall into one of three groups the lipoplethoric (obese adults who have little tendency to ketosis and respond readily to diet and to insulin), the insulin-deficient (children and young adults with ready tendency to ketosis), and the lipo atrophic (no fat depots liver disease, intense hyperlipemia, little ketosis, and insulin resistant) As a working hypothesis he believes that the lipogenic action of insulin cannot be effected in the first because fat depots are filled and glycosuria therefore appears in the lipo atrophic groups an inability to deposit fat is postulated

Summary

Insulin may act to accelerate the disposal of carbohydrate by facilitating the entry of glucose into cells, accelerating the phosphorylation of glucose and increasing the transformations within the Krebs cycle An important by product of the latter two effects is the production of high energy complexes of phosphorus It should be emphasized however that insulin does not initiate these reactions but rather alters the rates at which they occur This is in keeping with the knowledge that glucose utilization still occurs even though at a greatly reduced rate in the animal totally deprived of insulin

The administration of insulin without carbohydrate produces hypoglycemia which is accompanied by hypophosphatemia, hypokalemia and hyperchloremia in the nondiabetic In the diabetic these plasma constituents undergo directionally comparable changes which ultimately prove to be of the same magnitude as in the nondiabetic The rates at which they occur however are much slower The use of insulin and glucose in combination produces less of a decrease in serum inorganic phosphorus and in potassium in diabetics than in normals

It has been suggested that insulin glucose tolerance responses can be used to identify insulin sensitive and insensitive diabetics though the day-to day variations in such responses render this uncertain

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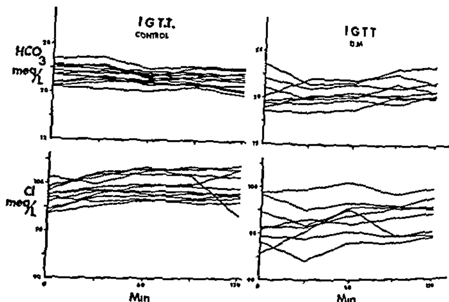


FIG 10-8 SERUM BICARBONATE AND CHLORIDE CHANGES FOLLOWING INTRAVENOUS GLUCOSE AND INSULIN ADMINISTRATION TO HEALTHY AND DIABETIC CHILDREN
The responses are comparable in the two groups (7e)

and Griffiths (17i) have pointed out that the diet and the control at the time of the test will convert the patient from one category to the other Recently, Anderson (17j) has suggested that failure to use glucagon free insulin as Himsworth did accounts for the test failures He believes a six minute tolerance test using pure insulin suffices for the classification and also points out that diet can change the patient from one category to the other

A The Inherent Variability of Glucose Insulin Tolerance Tests

The great variability in the disappearance of glucose following one type ... the complexity
5 gm of glucose
body weight In
mg per cent per
d in severe dia-
betes between 1 5 and 6 9 It is obvious, therefore, that in some diabetics mild or severe, the utilization of glucose is as high as it is in normals and no sharp separation on basis of sensitivity and insensitivity is evident Westphal has also pointed out that simple water deprivation produces a temporary but marked increase in insulin resistance (17l)

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regulation of the blood sugar concentration As the level of blood sugar rises, insulin output as reflected by the hypoglycemic effect in the recipient animal also rises Decreases in the level of blood sugar evoke in turn an increased release of the factor which raises the blood sugar The finding of hyperglycemic glycogenolytic principles in the extracts of various tissues may mean that pancreatic glucagon is transported and stored in these sites or, as indicated earlier that these factors arise therein and need not be chemically related to pancreatic glucagon The administration of I^{131}-labeled pancreatic glucagon results in a high concentration of radioactive protein in the kidney and lower amounts, in the order of descending concentrations in the thyroid blood liver duodenum, salivary glands and pancreas (6) It is probable that some of the hyperglycemic glycogenolytic factor which can be isolated from urine is glucagon but another principle must be present as well because Moy and Hoffman (7a b) have found that the urinary factor is much more active than pancreatic glucagon in stimulating glycogen breakdown in liver homogenates

1 Effects upon Intermediary Metabolism

In the diabetic rat glucagon produces only a transient increase in glycosuria (8a) Glucagon depresses the incorporation of acetate into liver fatty acids (8b) and the administration of glucagon to normal rats for brief periods of time inhibits the rise in liver fat and the ketonemia which accompany fasting (3b) It is of interest that under such circumstances the liver glycogen and blood sugar remain constant and the urinary nitrogen increases The last fact has already been cited (section III) as possible evidence for an effect of glucagon on gluconeogenesis In the intact force fed rat on a high carbohydrate diet glucagon increases blood sugar and glycosuria (8c) The last two sets of studies mentioned suggest that the biochemical effects of glucagon vary with the state of nutrition and the metabolic substrate

B Changes Following Prolonged Therapy with Glucagon

Galansino and others (9a) gave glucagon intraperitoneally to adult rats for periods of 14 to 104 days and noted no significant changes in the levels of serum cholesterol lipid and lipoproteins glucose tolerance and insulin tolerance were not altered the weight and appearance of the liver heart pancreas pituitary and adrenals were unchanged glycogen content of liver, heart and gastrocnemius muscle did not differ from that observed in controls*

Recently Best and colleagues have shown that depot glucagon has a diabetogenic action in force fed rats (9b)

* Root however has confirmed her earlier work in finding that glucagon increases liver glycogen under the conditions of her experiments (*Endocrinology* 59 340 1956)

III. Mechanism of the Hyperglycemic Effect of Glucagon

Burger and Kramer (1d) in their early studies reached the conclusion that glucagon acted directly on hepatic glycogen On theoretical grounds however, the rise in blood sugar following glucagon could result from liver deglycogenation with release of glucose, from increased gluconeogenesis from an inhibition of glucose utilization, or from conversion of muscle glycogen and lactic acid

A Studies of the Release, Production, and Disposal of Glucose under the Influence of Glucagon

The studies of Kibler and Myers (3a) showing that glucagon infusions produce an outpouring of glucose from the liver with no significant splanchnic urea production indicate that gluconeogenesis from protein (there are no data on fat) makes no important contribution but it must be pointed out that in fasting rats glucagon has been found to increase urinary nitrogen excretion (3b) The fact that arteriovenous blood sugar differences show no change following glucagon (3c, d) suggests that the hyperglycemic effect cannot be attributed to an inhibition of the peripheral utilization of glucose The intravenous glucose tolerance studies of Ingle *et al* (3e) in eviscerate rats also indicate that glucagon does not interfere with carbohydrate disposal On the other hand evidence has been advanced that glucagon enhances glucose disposal (3f)

There are no specific data on the effects of glucagon alone if any, on glycogen in muscle and other tissues, though it has been noted that in contrast to the epinephrine effect glucagon does not increase lactic acid levels (3g) When glucagon is given with insulin however it interferes with the muscle glycogenating effect of the latter (3h–k)

B Enzyme Systems Involved in the Hyperglycemic Effect of Glucagon

The demonstration by Sutherland and Cori (4a) that glucagon increases phosphorylase activity in liver slices as measured by glycogen synthesis identifies one of the enzyme systems involved Wosilait and others (4b–d) have shown that the concentration of active phosphorylase in the liver represents a balance between synthesis and inactivation and that the synthetic aspects of this balance appear to involve epinephrine and glucagon while inactivation is catalyzed by another enzyme The latter has been tentatively designated as the liver phosphorylase inactivating enzyme

IV. Physiologic and Biochemical Effects of Glucagon

The cross circulation experiments of Foa *et al* (5) indicate that the secretion of hyperglycemic glycogenolytic factor and of insulin is under the

C With Anterior Pituitary Adrenocorticotropin

Helmer and Root (12) have reported that in rabbits adrenocort enhances the hyperglycemic response to glucagon This is quite in with the known effects of adrenocortical steroids in increasing genesis interfering with the peripheral disposal of glucose, and fa the deposition of liver glycogen

D With Estrogens and Androgens

In rabbit studies the administration of folliculin produced con depression of the action of a hyperglycemic glycogenolytic facto from the pancreas whereas similar amounts of testosterone had (13a b)

VI Clinical Trials of Glucagon

Glucagon has been tried without benefit in Von Gierke s disease defects of phosphorylase action are known to be present (14)

Kirtley *et al* (15a b) have reported that in stable *i e* in in sensitive human diabetes glucagon produced a greater and more rise in blood sugar and a lesser serum phosphorus fall than in the or insulin sensitive The first of these observations would fit in well known observation that adequate stores of liver glycogen the control of diabetes but the second is more difficult to explain the labile diabetic is unable to dispose of as great a part of a carb load by glycogenation and therefore glycolysis which pre emp phorus is enhanced (see Chapter 9) Preliminary reports of si tempts to categorize diabetes on the basis of the response to gluca begun to appear (15c d)

VII Blood Sugar and Electrolyte Effects of Glucag in Diabetic Children

In preliminary studies we found that the administration of intravenously 16 gamma per kilogram of body weight produced rise in the 30 minute blood sugar level in seven out of eight diab dren and a delayed rise in the eighth (16) The magnitude of thi in five of the children was greater than that seen in the controls (fi and 11 2) These findings suggest that glucagon released glycog from the liver of each diabetic and that the greater rise was pro lated to a relative inability of the diabetics to dispose of the incr blood sugar This is supported by the tendency for the blood su

V. Interrelations of Glucagon and Other Endocrine Secretions

A With Insulin

It has already been indicated in section IV of this chapter that an inverse relationship appears to be present between the level of sugar or the output of insulin and the secretion of glucagon As might be expected insulin can ultimately cancel the hyperglycemic effects of glucagon (10a) The studies of Root Ellis and Staub (10b) quantitate the converse relationship i e [illegible] They found [illegible]

ing with this measurements of blood sugar levels in mice show that even with a 50 per cent glucagon admixture only the 15 minute point is higher than the pure insulin response In rabbits however there is a more marked blood sugar difference in that a one per cent glucagon admixture results in hyperglycemia at 15 minutes a return to the zero value at 30 minutes and no difference thereafter from the blood sugar curve obtained with pure insulin If a ten per cent admixture is used the glucagon plus insulin curve is higher for the first full hour and then identical with the glucagon free insulin decrease The effect of glucagon insulin mixtures in man has not been established

B With Anterior Pituitary Growth Hormone

A number of observations point to a relationship between glucagon and growth hormone Thus Bornstein Reid and Young (11a) found that administration of growth hormone resulted in the appearance of a hyperglycemic factor in the portal blood of alloxanized hypophysectomized adrenalectomized rats Cross circulation experiments by Foà *et al* (11b) support the same conclusion The administration of growth hormone has been shown to produce an initial transient hyperglycemia which has been attributed to a discharge of the alpha cells (see Chapter 2) Cavallero and Mosca (11c) reported that growth hormone increased the mitotic activity in the pancreatic islets and particularly in the alpha cells The pancreas of a dog in whom diabetes had been produced by five weeks of [illegible] (11d) showed marked granulation and enlargement of the [illegible] cells These and other [illegible] duces a hyperglycemic effect and changes in the alpha cells However in view of the cobaltous chloride alpha cell glucagon story (see section II) a direct relationship can only be postulated

C With Anterior Pituitary Adrenocorticotropin

Helmer and Root (12) have reported that in rabbits adrenocorticotropin enhances the hyperglycemic response to glucagon This is quite in keeping with the known effects of adrenocortical steroids in increasing gluconeogenesis interfering with the peripheral disposal of glucose and facilitating the deposition of liver glycogen

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In rabbit studies the administration of folliculin produced considerable depression of the action of a hyperglycemic glycogenolytic factor isolated from the pancreas whereas similar amounts of testosterone had no effect (13a b)

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VII Blood Sugar and Electrolyte Effects of Glucagon in Diabetic Children

In preliminary studies we found that the administration of glucagon intravenously 16 gamma per kilogram of body weight produced a distinct rise in the 30 minute blood sugar level in seven out of eight diabetic children and a delayed rise in the eighth (16) The magnitude of this increase in five of the children was greater than that seen in the controls (figure 11 1 and 11 2) These findings suggest that glucagon released glycogen stores from the liver of each diabetic and that the greater rise was probably related to a relative inability of the diabetics to dispose of the increment in blood sugar This is supported by the tendency for the blood sugar to remain elevated in the diabetics in contrast to the return to preinjection levels in the controls However the presence of a decrease in the serum

V. Interrelations of Glucagon and Other Endocrine Secretions

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effect and changes in the alpha cells However, in view of the [illegible] chloride alpha cell glucagon story (see section II) a direct relationship can only be postulated

measure and perhaps entirely from depolymerization of liver glycogen, gluconeogenesis from protein and especially from fat have not been definitely excluded nor has the question of possible interference with or facilitation of the peripheral disposal of glucose been unequivocally settled

The diabetic and nondiabetic both respond to glucagon with hyperglycemia though in the former the elevation in blood sugar persists However, such hyperglycemic responses cannot be cited as evidence for adequacy of glycogen stores in the diabetic, since interference with carbohydrate disposal or increased gluconeogenesis in the diabetic could mask an inadequate deglycogenation response

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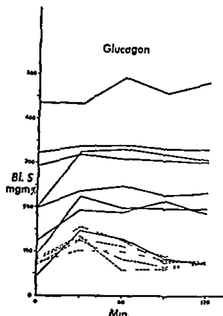


FIG 11 1 GLUCAGON INDUCED HYPERGLYCEMIA IN DIABETIC AND NONDIABETIC CHILDREN

In both the diabetic (solid line) and nondiabetic children (broken line) glucagon (16 γ per kg i v) induces comparable increments in blood glucose concentrations These persist longer in the diabetics (16)

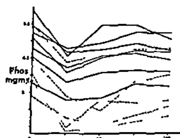


FIG 11 2 HYPOPHOSPHATEMIA FOLLOWING GLUCAGON ADMINISTRATION

The serum inorganic phosphorus decrease is about the same in teen-aged diabetics (solid lines) and teen aged or young adult nondiabetic control subjects (broken lines) following intravenous glucagon at zero time 16 γ per kg of body weight (16)

inorganic phosphorus concentrations in the diabetic (figure 11-2) indicates that phosphorylation and glycolysis were occurring though not to a degree sufficient to cancel the glucagon induced blood sugar rise

Summary

Glucagon or the hyperglycemic glycogenolytic factor of the pancreas acts upon liver glycogen The hyperglycemia which ensues results in large

measure and perhaps entirely from depolymerization of liver glycogen, gluconeogenesis from protein and especially from fat have not been definitely excluded nor has the question of possible interference with or facilitation of the peripheral disposal of glucose been unequivocally settled

The diabetic and nondiabetic both respond to glucagon with hyperglycemia though in the former the elevation in blood sugar persists However, such hyperglycemic responses cannot be cited as evidence for adequacy of glycogen stores in the diabetic since interference with carbohydrate disposal or increased gluconeogenesis in the diabetic could mask an inadequate deglycogenation response

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CHAPTER 12

Carbohydrate and Electrolyte Effects of Epinephrine

Prior to 1950 commercial preparations of epinephrine contained admixtures of norepinephrine Though these two amines are closely related structurally and possess the same general physiologic properties there are specific differences in their actions Some of these have been discussed in Chapter 3 (1a f) It may also be that their biochemical effects differ Hence in the discussion of the known carbohydrate and electrolyte effects of epinephrine which follows it must be kept in mind that the so called epinephrine studies conducted earlier than 1950 were actually based on the administration of epinephrine and norepinephrine The proportions of the two amines were probably four to nine parts of epinephrine to one part of norepinephrine (2a) since it is only in medullary tumors such as the pheochromocytomas that larger admixtures of norepinephrine have been found (2b c)

I Effects of Epinephrine and Norepinephrine on the Blood Sugar and the Glycogen of Liver, Muscle, and Other Tissues

The subcutaneous administration of epinephrine in a dosage of 0 01 ml of a 1 1000 solution in 0 9 per cent saline per kilogram of body weight produces an elevation in blood sugar Measurements of blood sugar concentrations at ½ hour intervals reveals a peak at 60 to 90 minutes and a subsequent return toward preinjection levels The magnitude and duration of this epinephrine induced rise in the blood sugar of a group of healthy teen age children and young adults in the fasting state is shown in figure 12 1 (3a b) The studies of Kroneberg and Romcke (3c) and of Kappert *et al* (3d) indicate that the hyperglycemic effect of norepinephrine is much less than that of epinephrine

Analysis of the liver skeletal muscles and other tissues for glycogen content routinely shows a decrease after epinephrine though the degree to which this occurs is variable (4a–c) It should be noted that insofar as the liver glycogen is concerned insulin (4d) pancreatic glucagon (4e) and other unidentified hyperglycemic glycogenolytic factors (4f)

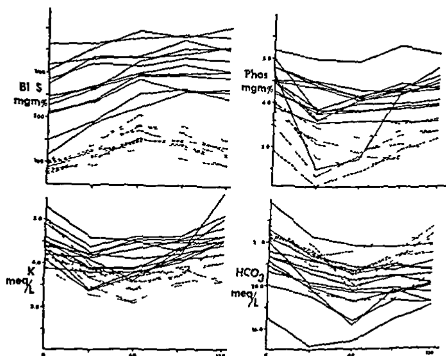


FIG 12 1 BLOOD SUGAR AND SERUM POTASSIUM PHOSPHATE AND BICARBONATE CHANGES FOLLOWING EPINEPHRINE

Dotted lines identify control studies in healthy teen-agers and young adults solid lines refer to results in teen-age juvenile diabetics The hyperglycemia is of comparable degree but persists longer in the diabetic The diabetics start with higher potassium and phosphorus values and as a group show less of a decrease The serum total $CO_2(HCO_3)$ responses are about the same (3a b)

also produce a depletion, but of these only epinephrine is known to reduce muscle glycogen (4g j) von Euler's findings (1b) indicate that norepinephrine has much less of an effect on muscle glycogen, since the rise in lactic acid is not as great as that produced by epinephrine

II The Mechanisms of Epinephrine Hyperglycemia

As in the case of any agent which induces hyperglycemia the rise in blood sugar produced by epinephrine may be the result of a) a shift in *dynamic equilibrium* leading to a depolymerization of liver glycogen b) it may represent increased gluconeogenesis or, c) it may be produced by an inhibition of the peripheral disposal of glucose Studies in patients with muscular dystrophy have raised an additional possibility d) muscle glyco

gen may contribute to hyperglycemia by conversion of lactic acid to glucose (2d, 3a b)

A Role of Deglycogenation, Gluconeogenesis, and Peripheral Blockade

It has already been indicated in the preceding section that epinephrine does indeed decrease liver glycogen (4a–c) However, it must be kept in mind that epinephrine may increase or decrease tissue glycogen including that of muscle, depending on the experimental variables, and the particular muscle glycogen fraction analyzed (4k–p) Insofar as the second point is concerned, there are data which indicate that gluconeogenesis from at least fat may be increased by epinephrine (4i–k) With respect to the third possibility, it has been shown by means of arteriovenous difference measurements (5a–c), and especially by means of glucose tolerance studies in eviscerated animals (5d), that epinephrine does inhibit the peripheral utilization of glucose, though earlier studies have been interpreted to indicate that this amine has no effect (5e f), or actually enhances the disposal of carbohydrate (5g) However, care must be taken to specify whether such enhancement of disposal represents glucose catabolism as herein intended or deposition of glucose as tissue glycogen (5h, i) Finally, in regard to the fourth point our studies in muscular dystrophy patients are compatible with decreased release and conversion of muscle lactic acid to blood glucose in the liver This is discussed further in section V of this chapter

The information available to date indicates therefore that at least three, and probably all four, of the possible effects contribute to the hyperglycemia which follows the administration of epinephrine Comparable data on norepinephrine are lacking

B The Enzyme Systems Involved

As pointed out in the chapter on glucagon, work in the Coris' laboratory (6a) and by others (6b–d) has shown that there are enzymes in the liver, phosphorylases which control the dynamic aspects of liver glycogenation and deglycogenation In one current view, epinephrine increases the level of phosphorylase by stimulating the synthesis of this enzyme rather than by inhibiting its inactivation, a role that has been assigned to the liver phosphorylase inactivating enzyme (6b, c) Though glucagon appears to have the same effect, it has not been established that an identical mechanism of action is involved Neither have the intermediate changes in muscle and in other tissue enzymes which produce deglycogenation and inhibition of glucose utilization been elucidated

III. Serum Phosphorus and Potassium Changes Following the Administration of Epinephrine

A Decreases In Serum Inorganic Phosphorus Levels

It has long been recognized that epinephrine produces a decrease in the serum level of inorganic phosphorus (7) Flock (8a), Soskin (8b) and their co workers, and De Venanzi (8c) have pointed out that studies in animals indicate that an intact pancreas is necessary for the decrease in serum inorganic phosphorus which follows epinephrine The resultant hypophosphatemia can in turn be taken to reflect glycolysis with attendant phosphorylation and perhaps other transfers of serum inorganic phosphorus The fact that entry of glucose into cells glycolysis and a decrease in serum phosphorus occur despite the epinephrine induced peripheral blockade of glucose utilization merely means that the net effect of the rise in blood sugar concentrations upon glucose entry into cells exceeds the net inhibitory effect

B Epinephrine Induced Hyperkalemia and Hypokalemia

Similarly, ample evidence is available that epinephrine produces a change in the serum concentrations of potassium An intravenous injection of epinephrine or perfusion of the liver with epinephrine releases potassium to the surrounding fluid D Silva and others have shown that if observations are made within several minutes of epinephrine administration, the serum potassium rises and falls or first falls and then rises and falls (9a–j) However at the 30 minute point a definite drop in serum potassium is always present (3a) The studies of Dury (10a) indicate that the decrease in serum potassium which is produced by insulin depends upon the presence of an intact adrenal but there are no observations comparable to those on serum inorganic phosphorus on the effect of pancreatectomy or destruction of pancreatic islets upon the potassium effect of epinephrine The origin of the hypokalemia following epinephrine remains obscure It may result from transfers out of the extracellular fluids into the tissues, and in part from increases in urinary excretion (7) Unpublished studies in this laboratory indicate that it cannot be attributed to dilution of the extracellular volume as a consequence of transfers of cell water

Epinephrine therapy protects animals against potassium intoxication (10b–d), whereas *in the adrenalectomized animal* epinephrine produces much more of a potassium decrease than in the normal (10e) The latter could be related to the absence of the adrenocortical steroids with removal of the steroid induced blockade of glucose utilization

As in the case of the blood sugar change norepinephrine induced hypokalemia is less than that which follows epinephrine (1b)

IV. Changes in Other Serum Electrolytes Accompanying the Decrease in Phosphorus and in Potassium

Detailed studies of the electrolyte responses of healthy control subjects in our laboratory have revealed that the epinephrine-induced hyperglycemia, hypophosphatemia, and hypokalemia are accompanied by definite decreases in serum total CO_2 content These are illustrated in figure 12-1 (3a, b) The mechanisms whereby these changes are produced by epinephrine have not been defined The serum sodium and chloride fluctuations have shown no predictable pattern of change

V. Effects of Hepatic and Muscle Disorders on Epinephrine Hyperglycemia and the Associated Electrolyte Changes

A In Laennec's Cirrhosis and Other Diseases of the Liver

In liver disease epinephrine produces less of a rise in blood sugar (10f, 11a–c), presumably because liver glycogen stores are depleted or less readily released The decreases in serum inorganic phosphorus, in serum potassium, and in serum total CO_2 content characteristically present at the ½-hour point in healthy subjects are on the whole less pronounced (figure 12 2) (10f) In Von Gierke's disease epinephrine does not produce hyperglycemia and this is utilized in the clinical identification of such infants (12)

B In Juvenile Muscular Dystrophy

Muscular dystrophy patients provide an opportunity to estimate the magnitude of the muscle contribution to epinephrine hyperglycemia In muscular dystrophy the hyperglycemic response to epinephrine is definitely less than in normal controls (figure 12 3) (3a, b) This could, of course, be the consequence of a deficit in or an unusual tenacity of liver glycogen stores, represent a diminution in the contribution from gluconeogenesis, if such there be, or result from an impairment of the usual epinephrine blockade of the peripheral utilization of carbohydrate As a fourth alterna-

nephrine is less This would result in a lesser release of lactic acid and less hyperglycemia after conversion to glucose 6 phosphate in the liver

VI. Epinephrine Tolerance Studies in Juvenile Diabetics

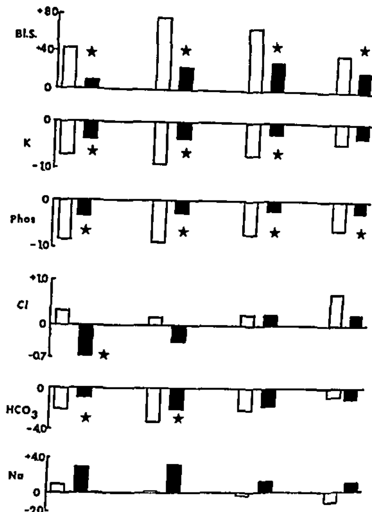


FIG 12 2 EPINEPHRINE RESPONSES IN CIRRHOSIS

Open columns represent average responses in healthy adults, solid columns identify studies in adult cirrhosis Statistically significant differences are starred The changes in blood sugar and in electrolytes are less marked in the cirrhotics (10f)

trols, averaging 35 1 and 37 7 mg per cent, at ½-hour (3b) It is to be noted that, compared to nondiabetics, the subsequent decrease in the blood sugar is less pronounced Directionally, the electrolyte changes resemble those seen in the nondiabetics, i e, the phosphate, potassium, and bicarbonate levels all fall, but the changes in the first two are of lesser degree These findings are presumably related to the more limited utilization of

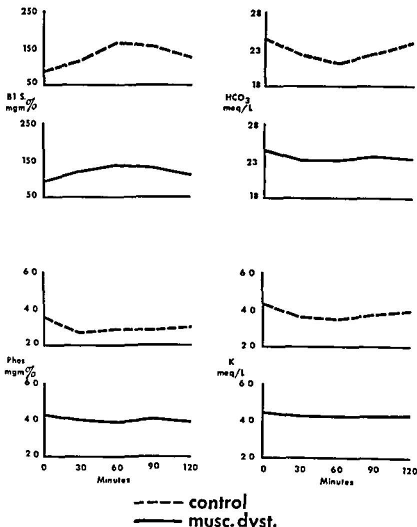


Fig 12-3 Epinephrine Tolerances in Muscular Dystrophy

In muscular dystrophy the hyperglycemia and the accompanying decreases in serum total CO_2 content (HCO_3), inorganic phosphorus, and potassium are less pronounced than in healthy control subjects (3a)

glucose in the diabetic and is in keeping with the persistence of the hyperglycemia

Summary

Epinephrine, like glucagon, activates liver phosphorylase (not necessarily in an identical manner) and results in deglycogenation of the liver In addition it decreases muscle glycogen and interferes with the peripheral disposal of glucose The last [illegible]

[illegible]

[illegible] rine-induced hyperglycemia represents the net result of release of liver glycogen, degradation of muscle glycogen with conversion of the resultant lactic acid to blood sugar in the liver, and peripheral blockade of glucose utilization Increased hepatic gluconeogenesis may also play a role

In epinephrine tolerance tests the diabetic responds with hyperglycemia equivalent to that seen in nondiabetics The interpretation of this as an index of liver glycogen stores is subject to the same limitations cited with respect to glucagon in the summary at the end of Chapter 11 In the nondiabetic the hyperglycemia is accompanied by a profound hypophosphatemia, hypokalemia, and a decrease in serum total CO_2 content In the diabetic these changes are less pronounced

In muscular dystrophy epinephrine produces less of a blood sugar and electrolyte response and the same is true in adult cirrhotics

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CHAPTER 13

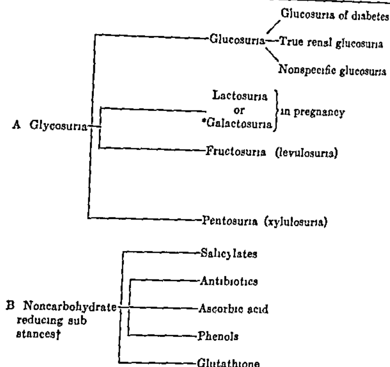
The Renal Glycosurias and True Renal Glucosuria

In general use phrases such as renal glycosuria, symptomless glycosuria, benign melliturıa, nonpancreatic glycosuria, and renal diabetes are nonspecific in that they are applied to patients who have reducing sugars in the urine without elevation of the blood glucose level above the usual fasting and postprandial limits (1a–i, 2a–l) Marble *et al* (2g, h) have suggested, however, that the designation renal glycosuria be applied only to patients a) in whom glucose is present in appreciable quantities in all urine specimens, even those obtained during the fasting state, b) in whom the fasting blood sugar concentration and the response to a test load of glucose as indicated by blood glucose levels, R Q changes, and the decrease in serum inorganic phosphorus are those of the nondiabetic, c) in whom insulin administration does not affect the glycosuria, and finally, d) in whom ketosis is more likely to develop on fasting than on overeating Though Marble's recommendations are reasonable and his criteria, with the exception of the last one are generally acceptable for the identification of this one type of glycosuria (2b, 3a), this entity requires a less confusing designation It might be better, for example, to use the phrase "true renal glucosuria" for this particular subdivision in the general category of glycosurias This custom will be followed in this chapter while the nondiabetics with occasional small amounts of urinary glucose will be designated as examples of nonspecific glucosuria The remainder will be referred to as examples of fructosuria, lactosuria, or pentosuria, depending upon the particular sugar present This classification leaves patients with noncarbohydrate reducing agents in the urine in a separate category (table 13 I)

I. The Frequency of Positive Tests for Urinary Reducing Substances of All Types in Nondiabetic Adults and Children and Their Causes

Routine tests such as those conducted on military inductees and on school children show an incidence of reducing substances in urine which ranges from 4 to 50 per thousand Thus Blotner and Hyde (2e) found 367 instances of melliturıa in 45,650 inductees, ranging in age from 18 to 45

TABLE 13-I



* or in galactose intolerance
† see text for others

years Wolman (2f) reported 296 in 77,293 trainees In school children Stuck (2j) obtained 81 positive tests in 1658 urine analyses

A Nature of Urinary Reducing Substances

In most instances apart from pregnancy the reducing substance present in urine is glucose with fructose (levulose) and pentose (xylulose), both of which are errors of metabolism, occurring next in the order of frequency In pregnancy in nondiabetics the usual sugar is galactose or lactose (2m)

a spillage of glucose and which are found only sporadically, herein re ferred to as nonspecific glucosuria, remain unidentified Some represent the initial manifestations of diabetes mellitus Others may fall into the

category of "Emotional Glycosurias' described by Cannon (1b) Undiagnosed hyperthyroidism (see Chapter 4) or other types of "physiologic alimentary glycosuria" account for a small number (2a) Some of the positive tests are blunders based on erroneous interpretations of the Benedict's test or the Clinitest

The remainder are false positives arising from reducing agents other than sugars, such as salicylates (2n) or antibiotics (2o) Other substances known to produce false positive tests include the glucuronides, ascorbic acid homogentisic acid, phenol, and glutathione (2p)

B Occurrence of Subsequent Diabetes in the Nonspecific Renal Glycosurias

It is obvious that the more precise and effective the criteria employed for the diagnosis or the exclusion of diabetes mellitus in patients first seen with so called nonspecific glucosuria, the less will be the subsequent incidence of diabetes mellitus in the remaining members of the group In the older studies from some clinics the figure ran as high as a 27 per cent incidence of subsequent diabetes (2q) In our own experience with some 500 nonspecific renal glucosurias which did not fulfill the criteria for diabetes, five subsequently developed diabetes (2r) This is in keeping with the favorable prognosis for accidental" glycosuria in insured persons reported by Marks (2u)

II. True Renal Glucosuria

In terms of renal dynamics the appearance of glucosuria in the face of normal levels of blood glucose cannot result from an increased glomerular filtration rate which in the human but rarely becomes supramaximal (2s) and must be the consequence of a decrease in the Tm_G, i e, a decrease in the tubular mass involved in the reabsorption of glucose (see figure 14-1 in Chapter 14) This has been shown to occur in true renal glucosuria and is at times associated with a decrease in Tm_{PAH}, i e, in the tubular mass involved in the secretion of para aminohippurate (2t)

A Incidence

Only a small portion of the renal glycosurias fall into the category defined by Marble and others (2g, h) and herein renamed true renal glucosuria At the Montreal General Hospital, Fowler (2b) classified only seven of 4000 cases of melliturua as true renal glucosuria The 82 cases seen at the Mayo Clinic (2c) were culled from a group of nonspecific glycosurias In Blotner and Hyde's series of inductees (2e) the 367 cases of melliturua proved to contain 33 true renal glucosurias, while the pro-

portion in Wolman's series (2f) was somewhat greater, 52 out of 296 The Joslin Clinic statistics show 53 out of 18,000 mellituria which fulfill Marble's criteria (2h) In Stuck's survey of school children (2j) 11 of the 81 renal glycosurics showed persistent reduction tests which could perhaps be classified as true renal glucosuria, but specific identifications of the reducing materials were not made A number of other workers have reported collections of cases ranging from four to 60 in number that appear to fulfill the criteria for true renal glucosuria (1a, f, h, 2i, k) In the series of children referred to us with uncharacterized glucosuria not of diabetic origin we have encountered one true renal glucosuria (2r) Results of glucose tolerance tests in a group of such patients are shown in figure 13-1 and are with but one exception within normal limits

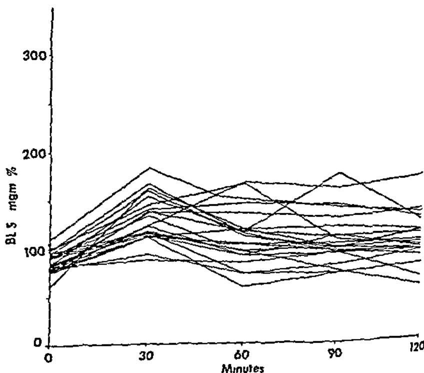


FIG 13 1 RESULTS OF ORAL GLUCOSE TOLERANCE TESTS IN NONSPECIFIC RENAL GLYCOSURIA

With occasional exceptions that are probably of no importance the standard oral tolerance test (1 75 gm per kg of body weight) yielded blood sugar curves with n the range of normal (mean ±1 SD) as established by studies in nondiabetic children (2r) However the highest value recorded at two hours (174 mg per cent) may represent a patient who has had renal glycosuria and is now developing diabetes mellitus

B The Clinical Significance of True Renal Glucosuria Not a Precursor of Diabetes Mellitus

It is obvious that the final test of true renal glucosuria as differentiated from diabetes mellitus is the failure of the patient to develop diabetes as the years go by Fowler (2b) even included in his criteria for true renal glucosuria the absence of a family history of diabetes, which seems a premature and at present an unjustified restriction It may well be for example that this entity does appear with greater frequency among diabetics, and in adhering to this additional criterion genuine cases of the disorder will be excluded This view is supported by recalling that Blotner and Hyde (2e) did find a 32 per cent incidence of a family history of diabetes in the 33 patients who fulfilled all the requirements for true renal glucosuria, and that diabetes mellitus and true renal glucosuria have been encountered in the same patient (see section C below)

The available experience indicates that true renal glucosuria may last a lifetime without the development of diabetes This was true of the cases cited by Marble in Joslin s text (2h) and in the 60 patients followed to date by Bansi (1g) It may also appear in one or more generations of a family Thus Brown and Poleshuck (1a) reported four cases of true renal glucosuria in three generations without ultimate evidence of deterioration of glucose tolerance Kramick (1i) has described an instance of true renal glucosuria of the familial type which appeared during childhood The largest series is that of Hjarne (3b) who found 34 cases in a kindred of 199 members

C Miscellaneous Conditions in Which True Renal Glucosuria May Occur as a Manifestation of Acute and Chronic Renal Disease

De Toni and Fanconi (4a–c) and others (4d–j) have described a syndrome in children with osteomalacia characterized by true renal glucosuria, increased renal output of amino acids and phosphate, and decreased serum levels of inorganic phosphorus resulting from a failure of normal reabsorptive processes in the renal tubule It may be associated with a renal tubular acidosis and also occurs in adult patients (4e, g, h, k) It can be hereditary (4j–m) Though uncommon, this entity appears sporadically on all pediatric services True renal glucosuria may also be observed in renal rickets (4n–q) characterized by azotemia, decreased urinary phosphate excretion, hyperphosphatemia, and hypocalcemia without an increased urinary output of amino acids These findings may also be encountered in the course of other types of nephritis unassociated with the abnormalities of bone growth characteristic of renal rickets Finally, true renal glucosuria can occur in the course of an otherwise uncomplicated pregnancy, during acute tubular damage, *i e*, a lower nephron nephrosis

(4r), and may coexist with diabetes mellitus (4s, t) or with diabetes and pyelonephritis (4u)

The chief importance of these miscellaneous renal glucosurias lies in not confusing them with the benign type (4v, w)

III. Fructosuria (Levulosuria) and Pentosuria (*Xylulosuria*)

In some individuals an ordinary intake of fructose results in a fructosuria (5a–e) This is a benign glycosuria which as far as is known has no immediate or long-term untoward effects

So called chronic essential pentosuria is also a benign glycosuria characterized by the more or less constant presence of xylulose (2 keto *D threo* pentose) (5f–h) in the urine in increased amounts (6a–u) Ribulose, another pentose, and xylulose are present in small amounts in normal human and rat urine, four and one milligrams per liter, respectively (6r) In a summary *published in 1943 Deruaux (6n) counted 163 cases of pentosuria in* the literature from 1892 up to that time, including the 149 collected by Enklewitz, Lasker, *et al* (6b, c, g) Almost all of the reported cases occur in Jews and especially in males, though at least one instance of a non Jewish background is recorded (6h) It may be hereditary (6g, q), has occurred in twins (6c), and has been found to occur concomitantly with true renal glucosuria (6p), migraine (6k, l), and progressive muscular dystrophy (6s, t) Scott and Cohen (6v) have reported on the origin and metabolism of ribose The utilization of pentoses in diabetes mellitus has *been discussed by Loos (6w), and the lack of a relationship between fruc*tose intake and pentosuria has been described by Flynn (6x)

IV. Identification of Urinary Sugars and Other Reducing Substances

A Glucose and Fructose

It is now possible to use an enzyme, glucose oxidase (supplied as Tes Tape® by Eli Lilly & Co and as Clinistix® by the Ames Co) which acts only upon glucose and which is readily available as impregnated tape to identify this sugar (7a, b) The usual procedure hitherto has been the fermentation with cakes of yeast (one quarter cake per two to four ounces of urine for several hours at 37°C) which will remove glucose and fructose completely, but *not galactose, lactose, or pentose* Particular care must be used to employ a yeast which ferments only glucose (7c) Special types of yeast can also be obtained which are specific for the fermentation of galactose and other sugars

If the fermentation test is positive, carrying out the Benedict's test at 50° to 60°C for 10 minutes as suggested by Lasker and Enklewitz (6i) or at room temperature for several hours (2g), will then differentiate between glucose and *fructose Only the latter of these* gives a yellow pre-

cipitate This test is not specific however for fructose since xylulose and large amounts of any reducing sugar, even glucose, will do the same However, if the sugar is completely fermented by ordinary baker's yeast, glucose and fructose can then be differentiated by Selivanoff s reagent (7d), consisting of 0 05 gm resorcinol in 100 ml dilute 1 2 hydrochloric acid or with the test described by Maurmeyer *et al* (7e)

The formation of osazones of fructose and glucose does not differentiate these two sugars since they have the same configuration at carbon atoms 3, 4, 5, and 6 and therefore have the same appearance and melting points In unpublished studies we have found that the D K spectrophotometer can be used to identify the untreated sugars themselves, since maximal absorption occurs at 360 and 390 mμ with glucose and fructose, respectively In our hands ascending paper chromatography (one dimensional) using butyl alcohol and water, octyl alcohol and water, or butyl and octyl alcohol produces no clear separation of these hexoses In phenol and water however R_f values of 30 and 50 are obtained for glucose and fructose, respectively

If the above procedures indicate that the reducing sugar is neither glucose nor fructose the tests described in the next section are then applied

B Galactose, Lactose, and Pentose (Xylulose)

The mucic acid test (2g) specifically establishes the presence of lactose and galactose and the presence of the galactose can be confirmed by a positive Tollen's test (2g 7f) In the latter, equal volumes of urine and hydrochloric acid (specific gravity of 1 09) and a small amount of phloroglucinol are added together and the mixture boiled Pentose, galactose, and glucuronic acid all yield a red color (7f)

Three procedures are available for identifying a pentose Bial s reagent (orcinol 1 5 gm , concentrated hydrochloric acid 500 ml , and $FeCl_3$ 20 to 30 drops (7f, g)) which yields a distinctive yellow color (2g), Wolfson's test (7h) in which the urine is treated with three per cent H_2O_2 to destroy 1 xylulose before running the Clinitest or the Benedict s test, and Tauber's procedure (7i) based on boiling the pentose in 0 5 benzidine solution and obtaining a cherry red color Glucose, fructose, and galactose produce yellow-brown colors

If identification remains uncertain after these relatively simple procedures osazone crystals can be formed by the use of phenylhydrazine for sugars other than fructose and methylphenylhydrazine for the fructose (7j) Save for the stereo isomers, the crystals formed from the various sugars under appropriate conditions have a characteristic appearance which, together with determination of their melting points following purification, makes the identification of the urinary sugar conclusive (8a–c)

Summary

On a probability basis the commonest reducing substance found in urine is glucose and the commonest cause of glucosuria is of course diabetes Galactosuria or lactosuria of pregnancy is next in order as a cause of urine tests positive for reducing substances Glucosuria present without undue elevation of the blood sugar levels is attributable to inadequate tubular reabsorption of filtered glucose and is designated true renal glucosuria in this text Usually this is not a prodrome of diabetes mellitus, though the two may occur in the same individual and instances of hereditary true renal glucosuria have been recorded True renal glucosuria may be present as a secondary manifestation in children with the DeToni-Fanconi syndrome as well as in patients with other forms of renal disease It has also been observed during uncomplicated pregnancy. The chief importance of fructosuria, pentosuria, and other true and false glycosurias lies in an accurate identification and avoidance of confusion with diabetes mellitus and true renal glucosuria

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CHAPTER 14

Therapy of Diabetes: General Consideration

One can speak freely only of one s own customs and views on the th
of diabetes but it is certain that all workers in this field whether
they have so stated have as their goal a long safe, and useful life fo
charges The fact that there are differences of opinion on how thi
be attained of itself indicates that no one approach has proved itself
superior to all others It is well to recognize that on the whole each
regimens in use at present can be made to meet the needs of the m
of a clinic s patients This should be viewed as an index of the adapt
of biologic organisms or of inherent margins of safety and not offe
scientific data which establish the merits of a particular system *With*
words of caution, a presentation of the current views of the author
his colleagues concerning the general principles of diabetic therap
those of others which concur or disagree will be undertaken

I. The Role of the Hospital in the Regulation of Diabe

It is not our custom nor that of most other clinics to hospitalize pa
simply for the regulation of diabetes Neither the time schedule
physical activity, the dietary customs, nor the emotional reactions
cate those outside the hospitals Admission should be reserved the
for the instruction of the families and patients, for control of di
during major infections, surgery, or dental extractions, for ther
ketosis and acidosis, and finally but not least important, for the reassu
of the patient An optional admission, just as a stay at a summer
does much to adjust the diabetic to his regimen, as he shares his l
and his experiences with others who have similar needs *This is a reas*
contrast to the atmosphere in a neighborhood, school or office
none of the others have diabetes Finally, a nontraumatic admission
enjoyable atmosphere minimizes the nonspecific turmoil attendant u
period of hospitalization necessitated by a complication

II Strict, Liberal, and Intermediate Regimens of Diabetic Regulation

A Regimens Aimed at Complete Control of all Symptoms and Signs of Diabetes

In some centers the goal in the therapy of diabetes includes relief of all symptoms continuation of normal rates of body growth in height and in weight, attainment of actual or virtual aglycosuria i e limitation of the 24 hour urinary glucose loss at or within five per cent of the carbohydrate intake and either demonstration of fasting and post prandial blood sugars within nondiabetic levels or limitation of undue hyperglycemia to the period following the noon meal (1a j 2a-e 3a-i) This degree of control is sought by measurement of intake use of mixtures of long and short acting insulins (1a-j, 3a-c) or multiple daily injections of rapid insulin (2a-e), and control of physical activity and exercise (2a-c)

Though achievement of this degree of regulation is the desideratum all of these workers admit that this is not always possible This is reflected in the grading systems applied in retrospect in evaluating the possible relation of severity of diabetes or the degree of control to the incidence of vascular and other complications (1j k) Thus Wilson Root and Marble (1j) suggest the following standards for excellent control 1) Patient must never have been in coma 2) Insulin was begun within a few weeks of the onset of diabetes 3) Urine tests for sugar made more than once daily ever since onset of diabetes with conscientious attempt to have the urine sugar free or nearly so before meals Insulin dosage adjustments determined by results of urine tests 4) Diet must have been weighed for at least 80% of the duration since onset of symptoms of diabetes 5) Regular physical

[illegible] sugar except for occasional traces very [illegible]

at ideal control

[illegible]ricted regimens

[illegible]s mellitus (2a)

In these programs insulin hypoglycemia is considered to reflect inadequate [illegible]

[illegible] and complete control of carbohydrate metabolism [illegible]

B Programs Emphasizing Elimination of the Immediate Untoward Effects of Unregulated Diabetes

In other clinics for children and adults it is felt that complete control of the type described above is either unattainable or involves restrictions which create emotional and psychologic disturbances These units emphasize freedom from symptoms, signs, and consequences of undue hyperglycemia and glycosuria as the chief aim Normoglycemia and aglycosuria are considered as constituting either unnecessary precision of control or goals not attainable without dangerous shocking (4a, b, 5a–c, 6a–c, 7a–c) Dietary restrictions are minimal, *i e*, food is not weighed nor measured but estimated from previous experience In support of this practice it is pointed out that when children are left to their own devices, following proper indoctrination and interdiction of obvious sweets, they select a *diet very much like that prescribed to other diabetics (4a, b) Insulin is* then given in accordance with nonburdensome schedules in amounts sufficient to eliminate polyuria and its concomitants and to provide adequate utilization of calories for growth Urine tests are used for this purpose and measurements of blood sugar levels are only employed for the resolution of special problems such as, for example, interpretation of glycosuria which does not adequately reflect the degree of glycemia Shocks are avoided Asymptomatic hyperglycemia and glycosuria are accepted without concern, since it is felt that so called complete control does not guarantee escape from the vascular complications of long-standing diabetes

It should be emphasized that though such regimens have been called "free," the term "normal" in the sense that these patients live in large measure as do their nondiabetic confreres provides a more accurate description (7a–c)

C The Compromise Between the Restricted and the Liberal Regimens

Many practitioners, not convinced of the value of the more rigid criteria of control or unable to apply them effectively, are loathe to provide a measure of freedom as large as that permitted in the liberal programs (8a, b) These workers attempt to compromise by combining the better features of both of the so called extremes

1. Current Practice of the Author and His Colleagues. We fall into this compromise category for a somewhat different reason Evidence is accumulating that the so-called normal diet of the nondiabetic American is not optimal It provides too many calories and too high a proportion of fat, or of certain fats in particular, and in all probability contributes to a rising incidence of vascular disease (9a–d) It may well be, therefore, that caloric restriction can offer some measure of protection to the diabetic

population which is already especially susceptible to cardiovascular complications

In our clinic diets which are first weighed and ultimately estimated are prescribed *The over all aim is to attain as complete control of glycosuria and of fasting and postprandial hyperglycemia as possible without manifest or subclinical insulin shock This is a reasonable goal in most juvenile diabetics* More rigid criteria such as virtual aglycosuria and normoglycemia inevitably result in hyperinsulinism and are not realistic This does not mean of course that there are no children in whom virtually all evidences of disturbed carbohydrate metabolism cannot be eliminated with safety They are unfortunately a small minority in contrast to their much larger numbers amongst the patients who develop diabetes in the later decades One definite feature that clearly separates the bulk of the adult diabetics from the juveniles is the greater fluctuations in the day to day *control in the latter Irrespective of whether this is the result of variations* in diet activity emotional status or other factors it does necessitate a less *tight degree of control in the young diabetic if margins of safety whereby* hypoglycemia can be avoided are to be available

2 How Realistic Is the Goal of Complete Regulation? It has already been pointed out that other workers believe that rigid control of juvenile diabetes can be achieved with safety (1a j 2a–e 3a–c) However it is certainly true that we as physicians are at times unwittingly deceived in at least some of these instances chiefly because the sampling of blood and of urine during visits represents a mere fraction of the total record of the metabolism of carbohydrate and other foodstuffs Each clinic has seen patients who go into training for *the trip to the doctor*

their test and relax until the next visit Granting however ...

ment? One must also ask what does extraction of such payments ... Can one speak with any certainty in promising that the reward will be freedom from severe vascular disease *after two or more decades of diabetes?* The proof that there is such a reward is far from convincing In the better known clinics *the evidence consists of a small* difference often of dubious statistical significance between two large groups of patients one with a satisfactory and the other with an unsatisfactory record of regulation each afflicted with major vascular disease (1a–d 1j 10a c 11a–c *12a–c* 13a b) This point is discussed in further detail in Chapter 23 and is introduced here only to provide a realistic basis for a philosophy *of treat*

ment based upon adults and children as intricate and variable biologic units

3 The Hazards of Hypoglycemia A few comments on the dangers of hypoglycemia are also in order It seems unjustifiable to look upon them as the necessary minor evils of approaching or attaining perfect control of the diabetic state Insulin shock can prove catastrophic The published reports (see Chapter 16) undoubtedly reflect only a fraction of the total incidence of fatal or permanently disabling sequelae of hypoglycemia It is also well to point out as others have done, that it is in itself productive of vascular lesions (see Chapter 16) and perhaps in some instances the correlation between the so called degenerative lesions of diabetes is with the episodes of hypoglycemia which occur in poorly regulated diabetics rather than with the hyperglycemia

III The Use of Blood Sugar Levels in the Regulation of Diabetes Mellitus

The expense and the need for visits to a laboratory or hospital render impractical the routine regulation of diabetes by serial blood sugar measurements Furthermore the nonduplicability of 24 hour blood sugar curves on successive days and the changes in the blood sugar levels under varying conditions of diet exercise emotion and insulin (14a, b) indicate that this may be too sensitive an index for routine use Similarly, we feel that the measurement of blood sugar levels at 6 to 12 week intervals during visits to the outpatient department represents an insufficient sampling to guide regulation Furthermore it necessitates an early arising, deferral of breakfast and prolongs the clinic visit We therefore rely heavily on urine testing for the routine regulation of the diabetic

Blood sugar levels are extremely useful however for the diagnosis of diabetes for identification of renal glycosuria and the differentiation of mellituria In the diabetic in turn such measurements are indispensible during emergencies created by infections or surgery or during complications such as acidosis or coma when urine tests cannot reflect the full extent of the disturbance This is also true in those patients in whom there is a discrepancy between blood sugar levels and urine tests as a result of diminished renal clearance of glucose or inadequate or incomplete emptying of the urinary bladder (see section IV which follows) Blood sugar determinations are also useful in pregnant diabetics when urine testing even after fermentation fails to clarify the degree of glucosuria and in diabetic patients with epileptiform seizures which must be differentiated from hypoglycemia

Whenever the clinical circumstances necessitate assessment of carbohydrate metabolism in the diabetic by blood sugar measurements the state

similar discrepancies can occur in the renal clearance of ketone bodies (16c)

B Nonrepresentative Urine Tests as Result of Incomplete Voiding

The second circumstance under which blood sugar levels are not reflected in the intensity of *glucosuria arises from an incomplete emptying* of the bladder or failure to fractionate the urine collection This masks hypoglycemia and aglucosuria interspersed between periods of hyperglycemia and glucosuria Thus measurement of the sugar in an overnight specimen may yield a two plus reduction when the blood sugar in the early morning hours is at normal or hypoglycemic levels The heavier spill shortly after retiring which masks this may be circumvented by collecting a specimen in the interval between arising and breakfast Unfortunately, *the errors resulting from incomplete emptying of the bladder* as a result of a neurogenic lesion of congenital or acquired obstruction are not so readily eliminated These are however rather infrequent

V. Use of Fractional and Premeal Urine Specimens in the Regulation of Juvenile Diabetes

Despite the above limitations urine testing does greatly facilitate the regulation of diabetes at home and during hospitalization for nonemergency *purposes such as indoctrination*

In the hospital the total 24 hour urine output is fractionated beginning in the morning by pooling all urine collected between 8-11, 11-4 4-9 9-6 and 6-8 o clock when meals are served at 8 00 a m, 11 30 a m, and 4 30
[illegible] degree of postprandial hyper
[illegible] re breakfast
[illegible] tone and di
acetic acid The fractions are then pooled for determination of the 24 hour glucose output *The small amounts removed for analysis* are inconsequential

Outside of the hospital urine testing can often be limited to before supper and overnight or before breakfast specimens since in the well regulated stable diabetic these suffice to indicate the efficacy of the before
[illegible] f short acting insulin
[illegible] useful in de
[illegible] of long acting
insulin or *of a mixture* of short- and long acting insulin [illegible] This subject is taken up in greater detail in section II of Chapter 16 In labile or poorly regulated diabetics more frequent testing can be used supplemented by examinations for acetone by means of Acetest® or Galatest® (17a-c) This and the Clinitest or the newly developed Tes Tape simplify testing away

from home (17d) On the other hand, stable patients whose tests are consistent find it possible to decrease the testing to several times each week

To eliminate pruritis and vulvitis female patients are instructed to bathe the vulva and perineum with lukewarm water after each voiding and gentian violet applications are prescribed if moniliasis develops (18) The local use of a one per cent hydrocortisone ointment relieves acute in flammation fungostatic antibiotics may also be applied

Summary

All programs of diabetic therapy in current use have as their goal a long and useful life free of complications This goal is sought under one of three current philosophies a) a strict regimen of control of dietary intake and at times of physical activity with sufficient insulin to assure normoglycemia during the 24 hour period, b) a so called liberal, free, or normal regimen without specific dietary prescription but providing enough insulin to keep the patient symptom free and to permit adequate growth, and c) an intermediate or compromise regimen in which diets are prescribed and and subsequently estimated with insulin given in as large quantities as possible without producing hypoglycemia Some workers believe that rigid control of diabetes with achievement of normoglycemia protects the diabetic against the vascular complications (retinopathy and nephropathy in particular) of long-term diabetes, though this view is controversial

We practice the compromise regimen because it has been our experience that the price of normoglycemia is frequent inadvertent hypoglycemia which is itself dangerous Also though the more rigid regimens may provide security for some patients they evoke rebellion in others We try, therefore, to achieve in our patients as complete control of diabetes as possible without producing hypoglycemia or imposing restrictions which unduly complicate the life of the patient This end is sought by teaching the patient and the family to make the necessary day-to-day adjustments in the regimen on the basis of serial urine tests Blood sugar measurements are not used routinely but reserved as guideposts in diagnosis and during complications

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CHAPTER 15

Therapy of Diabetes: Food and Diets

I Antecedent History

In the period just preceding the demonstration that a hypoglycemic factor could be regularly obtained from the pancreas and used to control diabetes (1a–d) it became evident that the survival of diabetics could be prolonged by diet alone provided that the intake of calories and of carbohydrate was restricted (1e f) In the nondiabetic such a diet of course, further curtails the disposal of carbohydrate (1g), presumably via all of the currently recognized pathways of carbohydrate metabolism, i e, glycolysis, the hexose monophosphate shunt and glycogen deposition In the diabetic, however, such carbohydrate and caloric restriction permits survival by virtue of the residual capacity for carbohydrate utilization and the ability of the organism to extract energy for metabolic needs from endogenous and exogenous fat

II Evolution of Current Dietary Practices

A Liberalization of Carbohydrate Intake and Abandonment of Dextrose-Fat Ratios

A number of different dietary regimens were advocated in the years following the general availability of insulin Some physicians still continued to emphasize carbohydrate restriction within amounts just sufficient to prevent starvation ketosis (1h i 2a–e), while others began to liberalize the intake (2f–j) Among the various diets permitting a higher intake of carbohydrate practically all possible quantitative combinations of carbohydrate and fat were employed Thus Joslin (2k) advocated a moderate carbohydrate and moderate fat intake Sprague *et al* (2l) used a moderate carbohydrate and high fat combination Adlersberg and Porges (2i) and Rabinowitch (2j) prescribed high carbohydrate and low fat regimens, and Butler (2m) limited the carbohydrate but not the fat and protein content

Subsequent studies have established that within certain limits the ratios of the carbohydrate, fat, and protein are not as important as the total caloric intake Thus Jackson and Kenefick (3a) have demonstrated that changing the fatty acid dextrose ratio of the diet without altering total

calories has no discernible effect on the fasting blood sugar and the insulin requirement However, reducing the carbohydrate content of the diet to levels low enough to result in ketosis *does decrease the ability to dispose* of carbohydrate (1g–1, 3b, c) The foodstuff source of the calories is also of importance in determining the satiety value of a diet, since this seems to depend in part upon the protein content (3d) Furthermore, it has been shown that the depth of postprandial hypoglycemic ' tail is greater after a high carbohydrate than after a high fat or protein diet (3e)

B Current Diet Prescriptions

At present those clinics and physicians employing diets in the treatment of adult diabetics prescribe a regimen moderately restricted in carbohydrate This is designed to provide about 1 gm of protein per kilogram of body weight and either an equivalent amount of fat, or fat in amounts sufficient to meet the patient's caloric needs (4a–f) In juvenile diabetes the same general pattern is followed save that the protein intake ranges up to 3 gm or more per kilogram and the total caloric need is calculated on either a body weight or an age basis (5a–i)

The enforcement of prescribed diets varies in different clinics Some rely on strict measurements of foodstuffs while others estimate the intake, employing tables of the preformed carbohydrate content of each item (5a g) *In others it is customary to start with measurements and transfer to estimates* (5h), or start with estimates and shift to an almost free diet (5i) Beaser (5j k) in a survey of 225 physicians treating adult and juvenile diabetics found that one third of them insisted that the patients weigh the food while the remainder accepted estimates based on household measures and exchanges

C The Advent of the American Diabetes Association Diet and the System of Food Exchanges

In 1950 the American Diabetes Association, the American Dietetic Association, and the United States Public Health Service devised a system which greatly simplified the preparation of diabetic diets (6) In this scheme foods which have the same amounts of carbohydrate, fat, or protein in a serving are arranged in groups The carbohydrate, fat, and protein content of the basic food items or of substitutes or *replacements which* are termed exchanges is shown in household measures in table 15 I A list of such exchanges for milk so that appropriate amounts of skim milk buttermilk, powdered milk etc , can be substituted is shown in table *15 II*
[illegible] per 100 gm , such
III) and are
15 IV) which
[illegible]hydrate and
includes beets, carrots, peas, and turnips [illegible]

TABLE 15 I*

Food values for calculating diabetic diets

Group	Amount	Weight	Carbohydrate	Protein	Fat	Energy
		grams	*grams*	*grams*	*grams*	*calories*
Milk, whole	½ pt	240	12	8	10	170
Vegetable, group A	as desired	—	—	—	—	—
Vegetable group B	½ cup	100	7	2	—	36
Fruit	varies	—	10	—	—	40
Bread exchanges	varies	—	15	2	—	68
Meat exchanges	1 oz	30	—	7	5	73
Fat exchanges	1 tsp	5	—	—	5	45

* Tables 15 I through 15 VIII rearranged from item 6 in references

2 gm of protein in 100 gm servings and is therefore included in the calculations Vegetables high in carbohydrate, such as beans, potatoes, and corn, are considered bread and cereal equivalents (table 15-V) Fruits have been listed in amounts which supply ten grams of carbohydrate (table 15-VI)

In the calculation and preparation of a prescribed diet the carbohydrate, fat, and protein of milk, of B vegetables, and of the fruits to be consumed in one day are subtracted from the dietary prescription The number of meat (table 15 VII), bread (15-V), and fat (15-VIII) exchanges in the remaining unassigned carbohydrate, fat, and protein are then obtained with the aid of table 15-I This scheme greatly facilitates the selection of dietary items and provides an approximately predictable intake of calories and of the chief foodstuffs As in any diet which is restrictive much can be

TABLE 15 II

Milk exchanges

Per serving carbohydrate 12 grams protein 8 grams, fat, 10 grams

Type of Milk	Approximate Measure	Weight
	cup (8 oz)	*grams*
Whole milk (plain or homogenized)	1	240
Skim milk*	1	240
Evaporated milk	½	120
Powdered whole milk	¼	35
Powdered skim milk (non fat dried milk)*	¼	35
Buttermilk (from whole milk)	1	240
Buttermilk (from skim milk)*	1	240

* Since these forms of milk contain no fat, two fat exchanges may be added to the diet when they are used

TABLE 15 III

Group A Vegetables

Negligible carbohydrate, protein, and calories if one cup (200 grams) or less is used

Asparagus	Eggplant	Lettuce
Beans, string, young	Greens	Mushrooms
Broccoli	Beet greens	Okra
Brussels sprouts	Chard, Swiss	Pepper
Cabbage	Collard	Radish
Cauliflower	Dandelion	Sauerkraut
Celery	Kale	Squash, summer
Chicory	Mustard	Tomatoes
Cucumbers	Spinach	Watercress
	Turnip greens	

accomplished by a high standard of cuisine and the use of condiments or of sweeteners such as saccharin In addition to the usual tablets the latter may also be obtained in a convenient liquid form (Sweeta®—Squibb)

D The Use of Free, Liberalized, or Normal Diets

1. Their Effectiveness in Controlling the Symptoms of Diabetes Physicians and clinics recognize that after a period on prescribed diets some of their patients abandon all measurements and estimations and merely partake to satiety of most of the foods on the family table Observations indicate that when children are given adequate amounts of insulin and left to their own devices they select diets which, while excluding items obviously high in carbohydrate, are quite similar in composition to those prescribed for many diabetics or eaten voluntarily by nondiabetic children of the same age (7a–c) These so-called normal diets suffice to

TABLE 15 IV

Group B Vegetables

Per serving carbohydrate, approximately 7 grams but see below, protein, 2 grams (1 serving = ½ cup = 100 grams)

Food	Carbohydrate Content
	grams/100 grams
Beets	8 0
Carrots	7 5
Onions	7 2
Peas, green (medium)	9 0
Pumpkin	5 1
Rutabaga	6 7
Squash, winter	4 9
Turnip	4 6

TABLE 15 V

Bread and cereal exchanges

Per serving carbohydrate 15 grams protein 2 grams

Food	Approximate Measure	Weight
		grams
Bread	1 slice	25
Biscuit roll (2 in diameter)	1	35
Muffin (2 in diameter)	1	35
Cornbread (1½ in cube)	1	35
Flour	2½ tbsp	30
Cereal		
Cooked	½ cup	100
Dry (flake and puffed)	¾ cup	20
Rice and grits cooked	½ cup	100
Spaghetti and noodles cooked	*½ cup*	*100*
Crackers		
Graham (2½ in square)	2	20
Oysterettes	20 (½ cup)	20
Saltines (2 in square)	5	20
Soda (2 ½ in square)	3	20
Round thin (1½ in diameter)	6–8	20
Vegetables		
Beans and peas dried cooked (Lima navy split pea cowpeas)	½ cup	100
Beans Lima fresh	½ cup	100
Beans baked no pork	¼ cup	50
Corn sweet	⅓ cup	80
Corn popped	1 cup	20
Parsnips	⅔ cup	125
Potatoes white—baked or boiled (2 in diameter)	1	100
Potatoes white—mashed	½ cup	100
Potatoes sweet or yams	¼ cup	60
Sponge cake plain (1½ in cube)	1	25
Ice cream (omit 2 Fat Exchanges)	½ cup	70

control all symptoms of diabetes and permit growth and development in children which appear to be as adequate as that seen with the more precise prescriptions (7a–c 8a–o) However, Uhry *et al* are concerned about the possible harmful effects of the high fat intake (8m) In addition Forsyth, Kinnear and Dunlop have pointed out that some of the patients do gain weight excessively (8p) and De Rodriguez has observed increased liver size and edema (8q)

In the minds of some workers these regimens are synonymous with entirely free or unrestricted diets though it is doubtful that any of the clinics have allowed the wide day to day variations in calories and in foodstuffs

TABLE 15 VI

*Fruit exchanges**

Carbohydrate—10 grams per serving

Food	Approximate Measure
Apple (2 in diameter)	1
Applesauce	½ cup
Apricots	
Fresh	2 medium
Dried	4 halves
Banana	½ small
Blackberries	1 cup
Raspberries	1 cup
Strawberries	1 cup
Cantaloupe (6 in diameter)	¼
Cherries	10 large
Dates	2
Figs fresh	2 large
Figs dried	1 small
Grapefruit	½ small
Grapefruit juice	½ cup
Grapes	12
Grape juice	¼ cup
Honeydew melon (7 in diameter)	⅛
Mango	½ small
Orange	1 small
Orange juice	½ cup
Papaya	⅓ medium
Peach	1 medium
Pineapple	½ cup
Pineapple juice	⅓ cup
Plums	2 medium
Prunes dried	2 medium
Raisins	2 tbsp
Tangerine	1 large
Watermelon	1 cup

* Unsweetened canned fruits may be used in the same amount as listed for the fresh fruit

high in carbohydrate which characterize the intake of the nondiabetic child and adult These successful moves toward liberalizations of the dietary regimen of the diabetic have clearly established that ordinary diets which provide adequate but not excessive quantities of calories suffice to regulate many diabetics They have also served to sharpen up the realization that the diabetic is primarily a person and not a bomb calorimeter that strict regimens may provide security to some patients and induce re

TABLE 15 VII

Meat exchanges

Per serving protein 7 grams, fat, 5 grams

Food	Approximate Measure	Weight
		grams
Meat and poultry, medium fat (beef, lamb pork, liver, chicken)	1 oz	30
Cold cuts (4½ in square, ⅛ in thick)	1 slice	45
Frankfurter (8 or 9 per lb)	1	50
Fish		
Cod, mackerel	1 oz	30
Salmon tuna crab	¼ cup	30
Oysters, shrimp, clams	5 small	45
Sardines	3 medium	30
Cheese		
Cheddar or American	1 oz	30
Cottage	¼ cup	45
Egg	1	50
Peanut butter*	2 tbsp	30

* Limit use or adjust carbohydrate (deduct 5 grams carbohydrate per serving when used in excess of one exchange)

TABLE 15 VIII

Fat exchanges

Fat—5 grams per serving

Food	Approximate Measure	Weight
		grams
Butter or margarine	1 tsp	5
Bacon, crisp	1 slice	10
Cream		
Light, 20%	2 tbsp	30
Heavy, 40%	1 tbsp	15
Cream cheese	1 tbsp	15
French dressing	1 tbsp	15
Mayonnaise	1 tsp	5
Oil or cooking fat	1 tsp	5
Nuts	6 small	10
Olives	5 small	50
Avocado (1 in diameter)	⅛	25

bellion in others, *and that factors other than diet*, such as emotional turmoil, have to be added to the previously recognized determinants of carbohydrate, protein and fat utilization, *i e*, exercise, *infection*, *status of* liver glycogen, et cetera

2. The Degree of Diabetic Control and the Incidence of Vascular Disease. *Presumably* liberalization of diets would by now have had wide acceptance were it not for the demonstration that juvenile and adult diabetics *surviving 15 or more* years show a high incidence of retinopathy and nephropathy (9a–m) which may prove disabling and even in the case of the latter, fatal Evaluations of their experiences led some workers to suggest that this complication is of greater frequency and severity in the less well controlled patients (9a–i) These clinics have remained advocates therefore, of dietary regimens which have as their goal a more rigid control of hyperglycemia and glycosuria It has been recognized, however, that even with this type of strict control such complications could not be completely averted Other physicians, including the author, feel that these vascular end results are either a function of the duration of the diabetes or that they represent a greater susceptibility which is inherited with the [illegible] ons are presented in [illegible]

and anxiety and that these are sufficient reasons for continuing a measure of dietary restriction In addition the author is of the belief that the so called normal diet of Americans is not necessarily optimal in the long term sense We do eat more than we need to meet activity requirements The studies of Ancel Keys and of others indicate that such excesses of caloric and of fat intake and perhaps of certain fats in particular, show a high correlation with at least one general group of the degenerative vascular diseases *i e*, arteriosclerosis (10a–d) *Recognizing that this category* differs in histology, distribution, and onset age from the retinopathy and nephropathy of diabetes, it may still be possible that the latter two are accentuated by an excessive intake Perhaps they can be prevented or minimized by limitations in the diet, or, as the studies of Kinsell *et al* suggest, by substitution of vegetable fat for animal fat (11a–d) Then too *the increasing height and size of the western population* looked upon as a harmless manifestation of the so called optimal *diet supplemented* by large volumes of milk may result, as McCance has suggested (12a), *in the same* [illegible] reason [illegible] r our [illegible] d in diabetic children and adults diets which are measured [illegible] household units and particularly emphasize the caloric and fat *content*

III Experience with Diets

1 *The Caloric Intake*

It is our custom to provide diets to satiety, *i e*, if the patient complains of hunger, the intake is increased The intake of carbohydrate is usually equally divided among the three meals with provision for between meal after play and before bedtime feedings Individual preferences or customs such as poor appetite at breakfast are taken into account in planning meals The average caloric intake at various ages and in relationship to body weight is shown in figures 15 1 and 15 2 These data are based on weighed diets as well as those estimated in terms of household measures for periods of one to twelve months The numbers of such periods in each category are listed in the legends to the figures

It is to be noted from figures 15 1 and 15 2 that the caloric intake in girls was less than in boys of equivalent age but comparable per kilogram of body weight In both groups the total calories rose with increasing age and body size but the intake per kilogram of body weight decreased pro

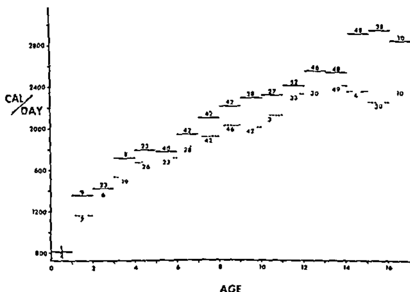


FIG 15 1 AVERAGE DAILY INTAKE OF CALORIES BY JUVENILE DIABETICS IN OUR SERIES

The males are identified by the solid and the females by the interrupted lines Super and subscripts indicate number of observation periods two to 12 months in length The male diabetics required a larger caloric prescription This difference became most pronounced in the 14 to 17 year-old group

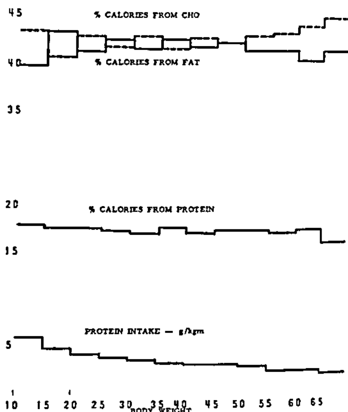


Fig 15-4 Intake of Protein and Percentage of Protein Carbohydrate and Fat in Children's Hospital of Pittsburgh Diabetic Diets Boys

Data are based on 453 diet periods in diabetic boys The find ngs are qu te comparable to those seen in diabetic girls as described in the legend to fig 15-3

weight of 55 kg In figures 15 3 and 15 4 it may be seen that protein provided about 17 per cent of the calories throughout this growth period while the remaining 83 per cent were obtained in equal proportions from carbohydrate and fat This is in keeping with the experience of others (12b)

We have not used fructose in the diets of our diabetic children Hartmann (13a) has reported on studies in five severe juvenile diabetics who were maintained on diets containing 25 per cent fructose or similar amounts of sucrose or glucose There was no [illegible] that the use of fructose in these amounts de[illegible] he insulin [illegible] Similarly in adult dia

betics there appears to be only a limited net gain in terms of urinary hexose excretion or of insulin need when fructose is included in the diet (13b) This means of course that the bulk of the administered fructose is converted to glucose during absorption, or if this does not happen, to liver glycogen and must ultimately be handled as glucose following glycogenolysis since it is well established that infusions of fructose, compared to glucose produce less of a rise in blood sugar a greater decrease in serum inorganic phosphorus, more of an increase in pyruvate and lactate, and less glycosuria (13c–f) Furthermore these advantages are all the more pronounced in diabetics (13g) and are to a great extent, though not entirely, still present in ketosis The use of fructose in acidosis and coma is discussed in Chapter 20

An adequate diabetic diet should provide a sufficient quantity of vitamins in the natural form However the interference with intake and the increased urinary volumes which inevitably occur from time-to time in most diabetics justify the regular use of a commercial polyvitamin preparation

As indicated earlier, evidence is accumulating that the incidence and intensity of atherosclerotic changes in populations as a whole are correlated not only with total calories but the proportion of fat in the diet. It seems probable therefore, that diabetic diets may also have too large an intake of fat *It seems reasonable to try in the next decade or two dietary* prescriptions which are lower in fat content and perhaps with the source of fat, *i e* animal versus vegetable and the type of vegetable fat specified in the hope of reducing the incidence of nephropathy, retinopathy, and arteriosclerosis in the diabetic

Summary

In the period just before the advent of insulin it was clearly demonstrated that total starvation during intervals of a week or longer, with water allowed as desired, decreased the hyperglycemia and glycosuria of diabetes The patient was then titrated for his ability to handle carbohydrate while on an allowance of 1 0 gm or more of protein per kg per day and fat in amounts sufficient for energy needs In this approach the emphasis was placed upon operating within the residual capacity of the patient to dispose of carbohydrate and other foodstuffs In many adult patients this is feasible without imposition of starvation regimens The greater caloric needs of the child for growth and the more complete character of juvenile diabetes (i e the lack of insulin is in all probability absolute rather than relative as it is in some adults) make it impossible to control diabetes by diet alone The availability of insulin permits the prescription of adequate diets The degree of dietary restriction varies

with the tenets of the particular clinic, i e, the diet may be specified in detail and closely followed by careful weighing of foods, it may be virtually unrestricted, or it may represent a compromise between these two extremes It is our practice to prescribe diets which are at first weighed and later estimated In view of the findings in nondiabetics the role of total caloric intake, and of the proportions and perhaps the type of dietary fat should be taken into account in devising programs to reduce the predominance of vascular disease in diabetics

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TABLE 16 I*

Approximate composition and properties of various insulin preparations

	Insulin	Globin Insulin with Zinc	Protamine Zinc Insulin	NPH Insulin
Physical form	Solution	Solution	Suspension—amorphous	Suspension—crystalline
Acidity	pH 3 0	pH 3 6	pH 7 2	pH 7 2
Zinc content per 100 units (mg)	0 03	0 3	0 2	0 03
Modifying agent per 100 units	None	3 8 mg globin	1 3 mg protamine	0 4 mg protamine
Isotonic agent	Glycerin	Glycerin	Glycerin	Glycerin + sodium chloride
Buffer	None	None	Sodium phosphate	Sodium phosphate
Preservative	Phenol or cresol	Phenol	Phenol or cresol	m cresol
Package	Cylindrical vial	Cylindrical vial	Cylindrical vial	Square vial

* From Jamieson *et al* (2f)

in table 16 II Analyses reveal that commercial insulin prepared without added zinc may but need not have this element present as an extractive of the pancreas, the addition of zinc, as in the manufacture of protamine zinc or globin insulin, understandably increases this amount The buffer employed influences the effect of the added zinc on the action of insulin Thus in Lente insulin prepared with acetate buffer the amount of zinc added is greater than that present in crystalline insulin made up in aqueous solution

4. Sites and Mode of Insulin Action The probable sites at which insulin exerts its effects upon carbohydrate metabolism have been discussed and illustrated in Chapter 1 In brief this hormone facilitates the entry and phosphorylation of glucose within cells The glucose 6 phosphate formed in this process can then enter the glycolytic cycle or the hexose monophosphate shunt with production of high energy phosphate and pyruvic acid, or be polymerized into glycogen after conversion to glucose 1 phosphate Insulin also facilitates the interconversions within the Krebs cycle, permitting the utilization of oxaloacetate formed from pyruvate by condensation with acetyl CoA derived from fatty acids for the generation of further amounts of high energy phosphate

5. Methods of Insulin Assay. A variety of methods have been em

TABLE 16 II*

Zinc content of various insulin preparations

Insulin Preparation	Zinc Content Per 100 Units	Other Constituents
Amorphous insulin	0 0 to 0 04 mg (USP)	No buffer
Zinc insulin crystals	0 016 to 0 04 mg (USP)	No buffer
NPH insulin	0 016 to 0 04 mg	1) 0 39 to 0 55 mg protamine per 100 u depending upon isophane point 2) Na_2HPO_4 buffer
Protamine zinc insulin	0 20 to 0 25 mg (USP)	1) 1 0 to 1.5 mg protamine per 100 u 2) Na_2HPO_4 buffer
Globin insulin with zinc	0 25 to 0 35 mg (USP)	1) 3 6 to 4 0 mg globin per 100 u 2) No buffer
Insulin semi Lente	0 2 to 0 25 mg	Sodium acetate buffer
Insulin Lente	0 2 to 0 25 mg	Sodium acetate buffer
Insulin ultra Lente	0 2 to 0 25 mg	Sodium acetate buffer

* After Peck *et al* (2g)

estimated on the basis of the last of these that the insulin content in the fasting blood of the rat is 10^{-5} unit per milliliter though the alloxanized hypophysectomized mouse technic detected none in pooled plasma insulin activity has been found in the beta globulins and lipoprotein of serum (2j, k) It should be kept in mind however that 15 minutes after an injection of I^{131} labelled insulin the highest radioactivity is in the tissues rather than in the plasma and in the kidney and muscles in particular (2o)

B The Onset, Intensity, and Duration of Action of the Various Insulins

In any discussion of the relative merits of particular forms of insulin, of special schedules of insulin administration or of the synchronization of insulin therapy with the distribution of the diet it is well to emphasize first that insulin itself is a wonderfully effective agent This tempers undue enthusiasm for what is new and permits a more objective judgment of the merits of variables which affect insulin action Such an attitude *facilitates impartial trials of alternative regimens and of newer versions* of the hormone The clinical features of the various types of insulin have been described in detail with supporting data by many workers Representative findings are cited in summary form in the sections which follow

1 Rapid acting Amorphous or Crystalline Insulin (Regular Insulins). For practical purposes the original amorphous and crystalline

attempts and those of others to use NPH for the control of diabetes during the school year were productive of severe nocturnal shocks reminiscent of those seen when protamine zinc insulin is used alone Presumably during the summer the exercise in camp helped control postprandial glycemia and glycosuria However this limitation of NPH insulin can be overcome by admixture of regular insulin in any proportion desired since it does not have an excess of a combining group We have used it with good effect alone or with regular insulin in a minority of our patients but as was pointed out earlier insulin in general is effective in diabetes

6 Lente Insulins The search continues for an ideal insulin *i e* one that duplicates in greater and greater numbers of diabetics the action of *endogenous insulin in nondiabetics The newest of these the Lente or* slow acting series (10a o) permits combinations with a spectrum of actions These insulins are all prepared with small amounts of zinc in an acetate buffer (10b f) Varying the proportion of the amorphous and of the crystalline forms of Lente insulin alters the onset peak and duration of action Lente itself is a 3 7 mixture of the amorphous and the crystalline forms of this zinc insulin and closely approximates NPH or a 2 1 mixture of regular and protamine zinc in its characteristics (10e) Increasing the amorphous fraction accelerates its action whereas raising the amount of the crystalline form retards it (10b) These modifications are currently undergoing clinical trials under the tentative designation of semi Lente and ultra Lente respectively It is recommended that the insulin be given ½ to ¾ of an hour before breakfast Stowers and Nabarro believe it can control 90 per cent of the adult diabetics but not during infections (10f) Gurling *et al* (10g) have used it in 45 children and have concluded with others *(10h–j) that there are some who cannot be maintained* on Lente alone This has been our experience as well We have also found that in *some children effective control can be achieved with a combination of* Lente and the short acting insulins In such mixtures Lente should predominate to insure preservation of the buffer mechanism (10k)

The relative activities of these various insulins are shown schematically in figure 16 1 (10p)

7 Other Insulin Types Though many other forms and modifications have been prepared and tested in commercial and other laboratories only a few of these results have been published (10q)

8 [illegible] Administration by Subcutaneous Pellet, *per os* or as An[illegible]

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years of age who were previously maintained on 40 to 100 [illegible] mine zinc insulin daily the pellets controlled three adequately *i e* with

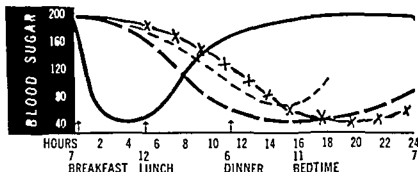


FIG 16-1 BLOOD SUGAR RESPONSES TO SHORT AND TO LONG-ACTING INSULINS

Regular or crystalline insulin (——) has a more prompt but less persistent effect upon the blood sugar curve than that exerted by lente (— —) globin (- - -) or protamine zinc (x x) insulins (10p)

only moderate hyperglycemia and glycosuria, and permitted the use of decreased insulin dosages in the others (10s)

Insulin *per os* in keratinized capsules was tried by Miller (10t) with possible blood sugar decreases If so this might have been the result of the production of an insulinase inhibitor of the type postulated by Mirsky *et al* (10u) as enzymatic digestion of the insulin molecule occurred In sulin given as an aerosol to rabbits is as effective as an injection (10v)

9 Insulin Adjuvants and Substitutes Insulin substitutes effective by mouth are announced at intervals The subject was reviewed in detail by Lewis in 1949 (11a) and recently Loubatières has called attention to

hypoglycemic effect Achelis and Hardebeck (11h) in investigating central nervous system effects produced by a sulfonamide derivative (N sulfanilyl N[1] butylurea or BZ55) noted hypoglycemia Franke and Fuchs (11i) tested this compound in nondiabetic and diabetic adults and found a blood sugar decrease which occurred in two to three hours Initial clinical trials with this agent in some 50 patients indicated that diabetic hyperglycemia and glycosuria could be effectively controlled without insulin in mild cases and the insulin requirement decreased in severe diabetes Bertram *et al* (11j) reported on 82 patients and concurred but pointed out that the drug was virtually ineffective in juvenile diabet ics The observation that the hypoglycemic response could not be elicited in pancreatectomized or alloxanized animals and the initial impression

of alpha cell damage (11h), not confirmed since, following administrati this material led to the suggestion that the compound acts by suppressi alpha cell and probably glucagon activity This however seems unli Instances where the hypoglycemic effect has not been elicited have attributed to a total lack of pancreatic insulin Bertram *et al* (11k) others abroad and in this country have since reported on the resul further studies with BZ-55, (Carbutamid), with *N-4-methyl be* sulfonyl-N[1]-butylurea (Orinase®), and related compounds (11l-w) keeping with the early impression these agents are most effective in patients with diabetes of recent onset characterized by a low insulin quirement and largely or entirely ineffective in juvenile diabetes, acic *or coma, infections, and pancreatectomized patients Withdrawal of* insulin substitute is usually followed in several days or weeks by a currence of diabetic symptoms or a rise in the insulin requirement

Possible sites of action suggested up to the present in addition to alpha cell suppression hypothesis include decreased absorption of ca hydrate from the gastrointestinal tract (11o), decreased gluconeogen (11l), increased hepatic glycogenation (11r), diminished glucose 6 pl phatase activity (11p), increased production of insulin (11q w), inhibi of insulin destruction via the insulinase-anti-insulinase system (11m and suppression of cytochrome oxidase activity *in vitro* and in the l (11v)

A 5 2 per cent incidence of side effects or toxic reactions has been *ported by the American distributors in 6,850 cases treated* with C butamid® "leukopenia (52 cases) and anemia (6 cases), skin rashes various types, including purpura and dermatitis exfoliativa (91 cases), the vascular system (16 cases) and interstitial myocarditis (1 case) addition, drug fever and a syndrome which is comprised of malaise lethargy, frequently accompanied by nausea and *vomiting have been* ported There have been four additional fatalities reported in which drug may have been implicated, although this is not entirely establishe and about one per cent in 4000 cases treated in Germany with Orina "mild in nature, urticaria, sensations of gastric fullness, and mild *tolerance to the ingestion of alcohol* * It is not possible at this writing predict the ultimate role of this class of insulin substitutes, but th *studies have surely* opened new vistas in the understanding of diabe and the possibility of more effective therapy

The intensity of experimental diabetes has also been shown to be

* ... and Co and the Upjohn Company ontinued reaction rate w han 10 000 American d abet

duced by salicylates and by agents derived from plants (11x-z) It cannot be assumed, however, that any agent or procedure which results in hypoglycemia is an insulin substitute This can be illustrated most clearly by indicating that severe liver damage or hepatectomy also results in hypoglycemia

II Initial Administration of Insulin to Newly-Discovered Diabetics: Antecedent History and Procedure

Customs vary in regard to the particular insulin, the dosage, and the schedules used in patients with newly-discovered diabetes not in acidosis or coma

A Antecedent History

Prior to 1937 multiple injections of regular insulin, up to four per day, were used practically universally in the therapy of juvenile diabetes (12a) From 1937 until the present the longer-acting protamine zinc or globin insulin has been used often in combination with the rapid acting forms (8g 12a–c) However, multiple injections of regular are still employed in some clinics (8g 12d e) In 1948 and in 1952, respectively, the first trials of the usefulness of NPH and Lente insulin in juvenile diabetes were undertaken (9b, 10g)



Fig 16-2 Average Daily Insulin Dosage in Diabetic Boys and Girls in Relation to Age

The numbers presented as ratios refer to periods of observation varying in length from two months to one year or longer

B Procedure

1. Past Experience with Regard to Insulin Need In starting a child on insulin it is our custom to use *the crystalline type first in fractions of* the amount which experience has shown approximates the need in the majority of the children in the patient's age group Thus it is evident from our data (figures 16 2 and 16 3 (12f)) and the reports of others (13a-c) that as the child increases in age and in body weight the insulin requirement rises In the group between 4 and 8 it averages 20 to 30 units rises to 30 to 40 units in the 8- to 12 year olds, approximates 40 to 60 units in the 12 to 16 year olds However, the scatter is extensive In terms of body weight the mean insulin dosage is one unit per kg (figure 16 3), but again the individual variations are great (figure 16 4) It is to be noted that the age of onset has no detectable influence upon the requirements in any particular age group, a finding previously noted by White (13a), and that there are no sex differences apparent in our series in contrast to the slightly greater requirement in boys reported by Jackson *et al* (13b, c)

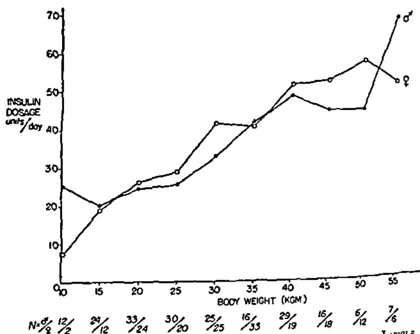


FIG 16-3 AVERAGE DAILY DOSAGES OF INSULIN IN JUVENILE DIABETICS OF VARIOUS BODY WEIGHTS

Ratios listed horizontally enumerate the numbers of periods of observation The steady rise at an approximate 1 1 rate i e 1 unit per day per kg of body weight is an average and is somewhat misleading since the range of variation is extensive

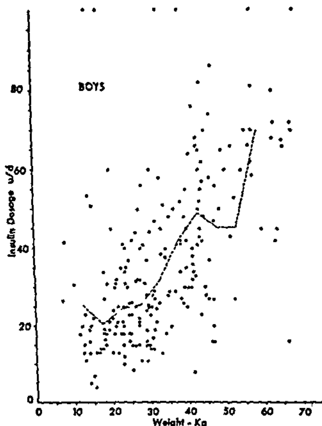


FIG 16-4 INDIVIDUAL DOSAGES OF INSULIN IN MALE JUVENILE DIABETICS IN RELATION TO BODY WEIGHT

It is obvious that the mean curve of insulin requirements in males shown in figure 16-3 and duplicated as a dotted line in the above figure is based upon a wide scattering of dosages

2 **Criteria for Prescribing Insulin Dosages.** The first dosage of crystalline insulin is approximately a quarter or a third of the presumed need and is given in the morning before the first meal of the prescribed diet The remainder is given before the mid day and evening meals, provided that abrupt decreases in glycosuria have not appeared If they do occur, the dosage is reduced On the other hand if glycosuria increases or if acetonuria appears the original estimates are raised and a before bedtime injection may also be given If this trial reduces the urine sugar output without pro-

ducing aglycosuria the patient is shifted to a mixture of protamine and crystalline, or NPH, or Lente alone or with crystalline on the next morning The quantity to be given is conservatively estimated as 80 per cent of the preceding day's dosage so that hypoglycemia may be avoided The proportions of the rapid acting insulin to longer-acting insulin in the mixtures is approximately two to one, but again this is a variable matter, given in one syringe without intimate admixture If the urine tests point to a gross insufficiency of insulin, additional amounts of regular insulin are given before one or both of the remaining two meals In subsequent days the urine tests are used as a guide in writing the insulin orders with particular emphasis on the before supper test as an index of the adequacy of the daytime control and on the overnight and before breakfast results in estimating nocturnal glycemia Blood sugar levels are measured at intervals and especially before breakfast as a check on the validity of the urine tests, but no attempt is made to obtain serial values throughout the day

If the newly discovered diabetic has ketosis or acidosis, then the regimen outlined in Chapter 20 is followed since in such patients the need for insulin is in excess of the ordinary day-to day dosage

III. Does the Diabetic Child Have To Continue on Insulin Indefinitely?

A The Rarity of "Reversible Diabetes" in Childhood

Instances of so called reversible diabetes are exceedingly rare in infants and in children (14a–f), and uncommon in adults (14g–j) Seven cases from the literature in which initially some or all of the criteria for the diagnosis of diabetes mellitus were present in infants are listed in table 16 III The blood sugar was elevated in at least three (14b, c, e), and in two of these regulation with insulin was undertaken (14b, c) Ultimately the signs and symptoms disappeared in all, and in those *receiving insulin the* requirement either decreased to zero or hypoglycemic shock appeared In one and possibly in two of these infants (14b, c) the disturbance of carbohydrate metabolism appeared in conjunction with an acute infection with attendant starvation This is also true, of course, in any series of permanent diabetics The subsequent course, however, was not that of usual juvenile diabetes, *i e* continued therapy with diet and insulin was not necessary It is therefore possible that these rare instances of reversible diabetes represent starvation, acute cerebral disease reversible acute pancreatitis or similar entities However, in view of the lack of sufficient data on these patients and the limited experience, it is best to set aside these individuals into a special category of unclassified disturbances of carbohydrate metabolism and not call them 'reversible diabetics ' This latter term only

TABLE 16 III

Transient or reversible "diabetes" in infancy

Authors	Ref	Age of Patient	Manifestation	Course
Ramsey	14a	4 wk 3 d	Polyuria hunger glycosuria	Normal tolerance at 5-7 mo
Lawrence, McCance	14b	18 d	Blue black spots glycosuria blood sugar 600 mg %, insulin ℞ 1 u q 4	Insulin not needed p̄ 5 d
Strandqvist	14c	1 mo	Purulent gangrene shoulder glycosuria, blood sugar 400 mg %, ℞ 2 u insulin	No further insulin p̄ 2 wk
Schwartzman	14d	< 1 yr	Transient diabetes in cited cases number 7 and 12	Recovery p̄ 3 mos and p̄ 6 wk
Arey	14e	15 d	Glycosuria, hyperglycemia, insulin ℞	Insulin stopped at age 2 mo
Keidan	14f	4 wks	Blood sugar 275 mgm %, impaired glucose tolerance and insulin response	Bl Sugar ½ hr p c 140 mgm % at 10 mos

tends to raise unjustifiable hope in families This is evident from the paucity of such cases in the interval since the first report in 1929 there have been approximately three generations of juvenile diabetics totalling one-half to one million children (see Chapter 7) or less than one reported instance of this unclassified carbohydrate disorder per 100,000 true juvenile diabetics

It may be that some of the children with these transient disorders of carbohydrate disposal will ultimately develop permanent diabetes In such instances it could be that an inherently limited capacity of the pancreatic islets to produce insulin was overwhelmed by or during the illness but that carbohydrate and insulin therapy permitted regeneration of the beta cells akin to that demonstrable in the experimental forms of the disease (see Chapters 2 through 6)

IV. Insulin Hypoglycemia

Insulin shocking occurs more often in children than in adults because juvenile diabetes is less stable and factors such as physical activity, emotional disturbances, onset and resolution of infections play a more prominent role than in the adult Because of the fluctuations in the diabetic state insulin hypoglycemia occurs more often in children on regulatory programs which have normoglycemia and aglycosuria as their goal

TABLE 16 IV

Similarities which result in confusion in the clinical and laboratory identification of insulin shock and diabetic keto acidosis

Insulin Shock or Hypoglycemia	Diabetic Ketosis-Acidosis
A *Coma may or may not be present*	A *Coma may or may not be present*
B Sudden onset in previously well diabetic, but does occur in poorly regulated and especially in so called brittle diabetics	B Less rapid onset, often in a poorly regulated diabetic, but can occur suddenly in a previously well controlled diabetic
C *Usually* not ushered in by infection, omission of food intake or increased physical activity may be antecedents, can be a blunder or deliberately induced as in an emotional disturbance	C Antecedent history of respiratory or other infection, onset of menses, emotional upset with or without increased food intake, or of insulin shock with loss of carbohydrate tolerance, omission of insulin
D Intercurrent infection or emotional upset with gastrointestinal symptoms may interfere with food intake	D Anorexia, nausea, vomiting and abdominal pain are present in 50-75% of the patients
E Occurs most often before meals	E May appear at any time
F Aglycosuria or mild glycosuria and ketonuria, but guard against confusion with urine formed earlier	F Profuse glycosuria and ketonuria but guard against confusion with urine formed earlier
G Blood sugar low if measured promptly, but hypoglycemic symptoms may follow relative rather than absolute decrease	G Blood sugar almost invariably elevated, but acidosis may rarely occur in virtual normoglycemia
H Serum total CO_2 content is normal, i e, higher than 20 mEq per liter, pH is normal	H Serum total CO_2 content is less than 15 mEq per liter, pH is normal at first and reduced later
I Respirations normal or shallow	I Respirations normal or shallow until hyperpnea, air hunger, and Kussmaul overbreathing set in
J Tachycardia, sweating with rapid acting insulin but not with the longer acting types, face pale, may convulse	J Tachycardia usually present and at times sweating as well, face red lips dry, no convulsions
K Responds to glucose therapy but this *may be slow especially* in severe shock of type seen with long acting insulin	K No prompt response to glucose but neither is patient made worse
L Insulin dosage to be adjusted downward	L Insulin is needed in large amounts

A The Recognition of Insulin Shock and its Differentiation From Diabetic Coma

Any symptom appearing in a diabetic child who is aglycosuric on insulin should suggest hypoglycemia In children maintained on rapid acting insulin the shocks are of sudden onset and usually occur during the day They are accompanied by clinical evidences of epinephrine discharge such as apprehension sweating tremors and tachycardia in addition to the mental confusion and unconsciousness which may develop With the longer acting insulins hypoglycemia tends to occur more often during the night and is usually unaccompanied by autonomic discharge (10h 15a) Unconsciousness and convulsions may be the first manifestations The patient and the family may be entirely unaware that shocking has occurred though malaise or headaches on arising should serve as a clue

The chief characteristics for the differential diagnosis of insulin shock and diabetic coma are listed in table 16 IV Usually these two complications are not confused if an adequate history can be obtained In its absence the physical findings and a representative urine analysis permit ready identification When in doubt glucose by mouth or by vein should be given since it will alleviate hypoglycemia and will not aggravate acidosis or coma It should be kept in mind however that in severe insulin shock recovery of consciousness may not be prompt even after blood sugar levels have been raised This should not be used as evidence against a loss of consciousness as a result of hypoglycemia Finally on occasion diabetics will develop illnesses unrelated to their diabetes such as epilepsy (15b) hyperventilation syndrome (15c) encephalitis meningitis barbiturate intoxication or cerebral thrombosis or hemorrhage These must be kept in mind as alternatives to insulin shock and diabetic acidosis in the production of unconsciousness in the diabetic

B The Occurrence of Spontaneous Hypoglycemia in Nondiabetic Children and Adults

Blood sugars of 50 milligrams per cent or lower during episodes suggestive of hyperinsulinism or following prolonged fasting (15d h) establish the presence of spontaneous hypoglycemia Results of glucose or of insulin tolerance tests are usually but not invariably confirmatory The hypoglycemia may have an endocrine basis (hyperinsulinism secondary to tumor of pancreatic beta cells or nesidioblastoma pituitary insufficiency as in Sheehan s syndrome or Simmonds disease adrenogenital syndrome hypoadrenocorticism as in Addison s disease or following withdrawal of steroid therapy or the rare entity of insulinoma with either parathyroid or pituitary adenoma or both) be hepatic in origin (Von Gierke s gly

cogen storage disease, *acute yellow atrophy and similar forms of toxic hepatitis*), occur secondary to central nervous system disease (lesions of the hypothalamus or brain stem), or represent an excessive sensitivity or response to presumably normal amounts of endogenous insulin (idiopathic *or functional hypoglycemia*).

The clinical manifestations resemble those of hypoglycemia secondary to overinsulinization as described in table 16-IV Carbohydrate feedings bring dramatic relief, and the electroencephalogram reverts to normal (15i, j) The elimination of endocrinopathy involving the pituitary or adrenal cortex and of hepatic or central nervous system disease as a cause for the hypoglycemia reduces the differential diagnosis to tumor of the islet cells or functional hypoglycemia Surgical exploration and removal of adenomata or subtotal pancreatectomy may provide a definitive answer (15h) Alloxan therapy is usually unsuccessful in the insulinoma but does work in functional hypoglycemia (15k, l) Cortisone or ACTH may control the hypoglycemia of either origin but is particularly useful in the treatment of the latter type in infants and young children (15e, m) High fat diets are only sporadically successful Fructose should be tried, particularly in the in-between meal feedings since it does not produce a hypoglycemic tail

C The Dangers of Hypoglycemia

Though recovery from insulin shock is usually prompt, the occurrence of *hypoglycemia is not to be taken lightly There are a number of reports* of hemiplegia, epilepsy, emotional disturbances, intellectual deterioration, and death attributable to insulin shock in diabetics of all ages (16a z, 17a b), including juveniles (16c, e, k, o, p–r, u–x, z) Hence in the treatment of *the diabetic child the prescription of insulin and of the food intake*, including in-between meal feedings, must be flexible enough to allow for the effects of exercise and inactivity, infection and recovery, and any other factors which alter insulin requirements

V. The "Brittle Diabetic"

This designation serves to identify diabetics whose course vacillates unpredictably between undue hyperglycemia-glycosuria-ketonuria and insulin shock At times it has been questioned that *such patients* actually exist and the controversy has been sufficiently intense to evoke the statement that there are no brittle diabetics, just brittle physicians whose attitude resembles that of the punitive parent

glycemia, hyperglycemia, etc On such regimens the liver becomes deglycogenated and ketosis supervenes Therapy consists of avoidance of *insulin shocking and pursuit of a dietary regimen which reglycogenates the liver, i e* adequate carbohydrate intake with provision for between-meal feedings Obviously this type of brittle diabetes is more apt to be encountered when a goal of complete control of all manifestations of diabetes is set up for patients whose status fluctuates from day to day

Unrecognized overinsulinization may also be present in patients who do not have such brittle characteristics These are detected only when the insulin dosage is reduced without *evidence of lessening of diabetic control It is wise, therefore, at intervals to try a reduction in the daily insulin* dosage to identify patients who are unnecessarily close to overt hypoglycemia

Finally, there are some patients who have liver disease such as cirrhosis or hemochromatosis which may interfere with adequate glycogen storage and release Even in these a more flexible regimen will often serve to eliminate brittle characteristics

VI The Extremely Young Juvenile Diabetic

The general principles of therapy (urine testing diet prescription, and insulin administration) discussed in this and the preceding two chapters are equally applicable to the infant or young child who develops diabetes A group of such patients, their ages of onset presenting symptoms, and therapy upon discharge *following the first hospitalization* are presented in tables 16-V and 16 VI *The youngest case on record is a male infant reported* by Guest in whom diabetes was diagnosed on the ninth day of life (18f-h)

VII. Insulin Therapy in Diabetics Undergoing Anaesthesia, Surgery, or Other Procedures Requiring a "Fasting" State

Whenever circumstances permit, patients who are to be *subjected* to anaesthesia and to surgical procedures should be transferred to rapid-acting insulin This will allow prompt readjustments in dosage in meeting any exigencies which may arise and avoid shock from excessive action of long acting insulin during periods of inadequate carbohydrate intake

As with any other surgical patient, such diabetics must be fasting insofar as *oral intake is concerned if the hazards of vomiting and aspiration are* to be avoided The diabetic should receive insulin, however, and an infusion of glucose in water prior to anaesthesia and surgery The insulin might equal two-thirds of the patient's usual dosage given one-half hour before the glucose, in terms of quantity the latter can approximate the obvious

cogen storage disease, acute yellow atrophy and similar forms of toxic hepatitis), occur secondary to central nervous system disease (lesions of the hypothalamus or brain stem), or represent an excessive sensitivity or response to presumably normal amounts of endogenous insulin (idiopathic or functional hypoglycemia)

The clinical manifestations resemble those of hypoglycemia secondary to overinsulinization as described in table 16 IV Carbohydrate feedings bring dramatic relief, and the electroencephalogram reverts to normal (15i, j) The elimination of endocrinopathy involving the pituitary or adrenal cortex and of hepatic or central nervous system disease as a cause for the hypoglycemia reduces the differential diagnosis to tumor of the islet cells or functional hypoglycemia Surgical exploration and removal of adenomata or subtotal pancreatectomy may provide a definitive answer (15h) Alloxan therapy is usually unsuccessful in the insulinoma but does work in functional hypoglycemia (15k, l) Cortisone or ACTH may control the hypoglycemia of either origin but is particularly useful in the treatment of the latter type in infants and young children (15e, m) High fat diets are only sporadically successful Fructose should be tried particularly in the in-between meal feedings since it does not produce a hypoglycemic tail

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[illegible]

ment that there are no brittle diabetics, just brittle physicians [illegible] titude resembles that of the punitive parent

The commonest cause of *brittle diabetes is unrecognized* insulin hypoglycemia which is followed by a hyperglycemic phase (18a–e) This in turn leads to further increases in insulin dosage with recurrence of hypo

glycemia, hyperglycemia etc On such regimens the liver becomes deglycogenated and ketosis supervenes Therapy consists of avoidance of insulin shocking and pursuit of a dietary regimen which reglycogenates the liver i e adequate carbohydrate intake with provision for between-meal feedings. Obviously this type of brittle diabetes is more apt to be encountered when a goal of complete control of all manifestations of diabetes is set up for patients whose status fluctuates from day to day

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As with any other surgical patient such diabetics must be fasting insofar as oral intake is concerned if the hazards of vomiting and aspiration are to be avoided The diabetic should receive insulin however, and an infusion of glucose in water prior to anaesthesia and surgery The insulin might equal two thirds of the patient s usual dosage given one half hour before the glucose, in terms of quantity the latter can approximate the obvious

TABLE 16 V

Onset symptoms and therapy of diabetes in infants and children 9 mos up to 2 years of age

Patient	Sex	Age	Onset Symptoms	Body Wt Discharge	Diet at Discharge				Insulin at Discharge*
					Calories	C	P	F	
		mo							
L M	F	9	Admitted in coma	7 7	General				P-4 R 2 a m R-4 p m
D D	F	10	Irritability, nocturia, polyuria, drowsiness	9 1	800	85	65	25	P 2 R-4
L C	M	11	Vomiting, overbreathing, weakness	8 1	1030	100	45	50	P-5 R-4
T C	F	11	Polyuria, polydypsia	8 6	1160	150	40	45	R 10 a m R-4 p m
L L	M	11	Polyuria, polydypsia	10 8	1210	125	40	35	P-4
S A	F	12	Weight loss, rash on buttocks, irritability, polyuria	9 8	1154	100	58	58	L 9
J D	F	12	Polyuria, polydypsia	14 4	1275	120	75	55	P 2 O-3 R-O-3
R H	M	12	Polydypsia, polyuria, irritability		963	63	51	51	R-5 R-4 R t i d
L W	F	14	Weight loss, irritability, polydypsia, diarrhea, nocturia, polyphagia	8 6	1170	125	46	45	R 10 a m R p m
M F	F	14	Vomiting, weakness	11 2	1514	153	68	70	L-4
J L	F	14							R 20
R W	F	15	Irritability, polyuria, polydypsia	8 6	1055	95	55	45	R 1 NPH 5
T C	M	15		11 0	925	105	40	35	P 2
C L	F	15	Weakness, polyuria, polydypsia, constipation	10 4	1290	172	38	50	R-5 a m R-[illegible] p m
L O	F	16	Polyphagia, irritability, polyuria, polydypsia	9 6	1252	118	60	60	P 2 R 7
J P	M	18	Weight loss, polydypsia, polyuria, polyphagia	11 5	1370	130	55	70	P-6 R 2
R R	M	19	Polyuria, polydypsia, irritability, weight loss, nocturia, polyphagia	12 5	1330	120	55	70	R-8

TABLE 16 V (Continued)

Patient	Sex	Age	Onset Symptoms	Body Wt Discharge	Diet at Discharge				Insulin at Discharge*
					Calories	C	P	F	
		mo							
T S	M	20	Listless polyphagia polyuria polydypsia	12 0	1502	151	67	70	NPH-8 R-4
A B	M	20	Polyphagia polyuria polydypsia weight loss	9 6	1310	100	70	70	P 2 R-3
D C	M	20	Polydypsia vomiting polyuria polyphagia		1252	118	60	60	NPH 15 R 1
V G	F	20	None	13 2	1130	130	40	50	P 4 R 3
D L	F	20	Rash on legs polyuria polydypsia	11 1	1100	110	30	60	P-5 R 17
J E	F	21	Weight loss polyuria polydypsia	11 6	874	80	50	26	R 15 a m & p m
T H	M	21	Polyuria irritability polydypsia weight loss irritation	12 2	1290	140	45	50	P 2 R 2
J J	F	21	Polydypsia drowsy weight loss polyuria	10 9	1000	120	40	50	R 2 a m & p m
T M	M	21	Diarrhea polydypsia vomiting	10 2	1502	151	67	70	P-3 R-5
M H	F	22	Irritability polyuria polydypsia	12 2	1200	660	180	450	P 2 R 2
B S	F	23	Nocturia polyphagia polydypsia	15 0	735	60	45	35	P 10 R-5
M O	F	23	Polydypsia nocturia	14 5	1385	140	60	55	

* P R L NPH and G refer to protamine zinc regular lente NPH and globin insulin respectively the sequence identifies schedule of injections Multiple injections have since been eliminated in our series

carbohydrate in the patient s usual breakfast given as a 10 per cent solution in water if time permits or in more concentrated form if necessary Invert sugar will minimize renal spillage At the end of the surgical procedure or during it if it is unduly prolonged the patient should receive the remainder of his insulin or a portion thereof, and the infusion of carbohydrate should be repeated With many procedures as with dental extractions or circumcisions the patient is usually able to resume oral intake by several hours The prescription of additional dosages of insulin

TABLE 16 VI

Onset symptoms and therapy of diabetes in children in the 3rd year of life

Patient	Sex	Age	Onset Symptoms	Body Weight at Discharge	Diet at Discharge				Insulin at Discharge*
					Calories	C	P	F	
		mo							
B B	M	24	Polyuria, polydypsia, polyphagia						R 6 a m R-6 p m
L M	M	25	Rash on legs, polyuria, polydypsia						
L C	F	25	Polyuria, polydypsia, polyphagia	13 4	1590	175	65	70	P 15 R 14
T L	M	27	Weight loss, polydypsia, irritability, nocturia, polyuria, drowsiness	14 7	1195	125	50	55	
K S	M	27	Polyuria, polydypsia, weight loss	12 8	1829	181	85	85	NPH 15 R-3
S D	M	27	Polyuria, polydypsia, *drowsiness*	14 4	1370	180	50	50	R 10 P-4
C D	F	28	Irritability, weakness, polyphagia, polyuria, polydypsia	13 6	1100	110	55	50	P 5 O-8 R-4 O-8
J P	M	29	Weight loss, polyuria, polydypsia, weakness		1175	115	55	55	R 2
F N	M	30	Polyphagia, polyuria	14 2	1445	150	65	65	P 2 R 9
R B	M	30	None	17 7	1105	130	45	45	P-4 R-3
D H	M	31	Listless, polydypsia, weight loss, polyuria	11 6	1829	181	85	85	P-4 R 10
C R	F	31	Weight loss, nocturia, irritability, polydypsia	11 5	1230	100	50	70	P 6 R-5
C S	F	31	Weight loss, polydypsia, fatigue, polyuria, nocturia, irritability	13 6	1230	120	50	60	R-3 P-3
P B	F	31	Weight loss, irritability, constipation	11 6	1505	170	60	15	P-6 R 14
R S	M	32	Weight loss, listless, polyuria, nocturia	15 9	1260	120	42		P 6 R-3
J M	M	33	Polyuria, polydypsia, drowsiness	15	1570	165	70	70	R-4 P-3
G S	M	33	Polydypsia, weight loss nocturia, irritability	18	1750	220	60	70	R 28 P-6
H T	M	33	Polyuria, listless, polydypsia	16	1570	175	60	70	P 2 R-4

TABLE 16-VI (Continued)

Patient	Sex	Age	Onset Symptoms	Body Weight at Discharge	Diet at Discharge				Insulin at Discharge*
					Calories	C	P	F	
		mo							
R D	M	33	Weight loss, polyuria, polydypsia	12	830	110	30	30	R-5 a m R 5 p m
C P	M	34	Weight loss, polyuria, nocturia, polyphagia	19 5	1754	170	70	86	P 12 C 14
R P	M	34	Weight loss, listless irritability, polyuria, polydypsia	14 7	1695	250	50	55	P 2 R-8
F G	F	34	Polyuria, polydypsia, weight loss nocturia	16 4	1350	130	50	70	R-5 O-4 R-3 O-4
M M	M	35	Fatigue, irritability, weight loss, polyuria	13 8	Measured				R 5 b i d
V M	F	35	Polyuria, dry skin, polyphagia polydypsia	11 9	1200	150	50	45	G 10

* P, R, L, NPH, and G refer to protamine zinc, regular, lente, NPH and globin insulin, respectively, the sequence identifies schedule of injections Multiple injections have since been eliminated in our series O refers to no insulin at noon on t i d injection schedule

should be guided by the results of urine analyses for glucose and acetone or by results of blood sugar measurements As pointed out in Chapter 14, blood sugar and serum CO_2 analyses and estimates of serum ketone levels prior to, during, and following surgery make possible a more precise control of the diabetic state (19a–c)

A Miscellaneous Procedures Requiring a Fasting State (GI Series, BMR)

Radiologic examination of the gastrointestinal tract of the diabetic can be carried out with the insulin infusion procedures described for surgery, or lactose can be incorporated into the barium swallow in amounts equal to the obvious carbohydrate in the patient's usual morning intake This again should be preceded by insulin, though in amounts less than the patient's customary dosage

Measurement of the basal metabolic rate in patients on insulin is probably an entirely useless procedure, since the rate of metabolic activity will depend on the residual insulin action and the substrate upon which

the patient is subsisting For evaluation of thyroid function the serum protein bound iodine (see Chapter 21) or tracer amounts of I^{131} should be used

Summary

The administration of insulin facilitates the entry of glucose into cells and accelerates phosphorylation, thereby permitting its storage as glycogen or entry into the glycolytic pathway Pyruvic acid, a product of glycolysis, can then be converted to lactic acid, alanine, acetyl CoA, or oxaloacetate The last of these enters the Krebs cycle by reaction with acetyl CoA derived from glycolysis or from the beta oxidation of fatty acids Insulin may also act to facilitate the conversions in the Krebs cycle and the formation of high energy phosphate compounds

In contrast to the adult diabetic who can often be controlled on diet alone, the juvenile diabetic almost always requires insulin The average dosage is one unit per kilogram of body weight but extensive deviations from this value are frequently seen The actual dosage is determined by the results of serial urine testing The before-supper and the before-breakfast tests point to the adequacy or inadequacy of control of postprandial and overnight hyperglycemia Combinations of rapid acting and protamine zinc or NPH insulins have had the most extensive usage in this country as well as in our clinic, though successful control on multiple injections of short-acting insulin or on globin insulin alone or in combination is possible *More recently Lente insulin alone or in* combination with rapid acting insulin has been introduced in the course of a search for an insulin which will meet the needs of the largest number of diabetics In the use of any insulin, hypoglycemia is to be avoided because of the central nervous system damage and vascular disease which it may produce It may also lead to so called brittle diabetes

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the patient is subsisting For evaluation of thyroid function the serum protein-bound iodine (see Chapter 21) or tracer amounts of I^{131} should be used

Summary

The administration of insulin facilitates the entry of glucose into cells and accelerates phosphorylation, thereby permitting its storage as glycogen or entry into the glycolytic pathway Pyruvic acid, a product of glycolysis, can then be converted to lactic acid, alanine, acetyl CoA or oxaloacetate The last of these enters the Krebs cycle by reaction with acetyl CoA derived from glycolysis or from the beta oxidation of fatty acids Insulin may also act to facilitate the conversions in the Krebs cycle and the formation of high energy phosphate compounds

In contrast to the adult diabetic who can often be controlled on diet alone, the juvenile diabetic almost always requires insulin The average dosage is one unit per kilogram of body weight but extensive deviations from this value are frequently seen The actual dosage is determined by the results of serial urine testing The before-supper and the before-breakfast tests point to the adequacy or inadequacy of control of postprandial and overnight hyperglycemia Combinations of rapid acting and protamine zinc or NPH insulins have had the most extensive usage in this country as well as in our clinic, though successful control on multiple injections of short-acting insulin or on globin insulin alone or in combination is possible More recently Lente insulin alone or in combination with rapid-acting insulin has been introduced in the course of a search for an insulin which will meet the needs of the largest number of diabetics In the use of any insulin, hypoglycemia is to be avoided because of the central nervous system damage and vascular disease which it may produce It may also lead to so-called brittle diabetes

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CHAPTER 17

Regulation of the H^+ Concentration of Body Fluids: the Effects of Uncontrolled Diabetes Mellitus

The hydrogen ion concentration, *i e* the pH, of body fluids is maintained at a slightly alkaline level by a) buffer systems which minimize the yield of H^+ or OH^- ions from inorganic and organic compounds and b) regulatory systems (the lungs and the kidneys) which restore the buffers and H^+ concentration to normal by judicious conservation or excretion of body fluid constituents Though it is still not clear why in the course of evolution the hydrogen ion concentration of body fluids became fixed at this particular level rather than at any other our knowledge of how such levels are maintained constant by the above mechanisms in health and altered in disease states is steadily expanding Information germane to an understanding of the changes which may occur in the diabetic is discussed in outline form in this chapter It should provide a suitable background for effective reference to texts, monographs and other publications in which this complex subject is treated in greater detail (1a 1)

I. The Buffer Systems of the Body

A buffer system consists of a weakly ionized acid, or in modern terminology a proton donor, i e a substance which in solution yields a relatively small amount of H^+ ions or protons, and a salt of that proton donor The relative proportions of the two components of a buffer system determine the H^+ ion concentration thus the greater the concentration of the salt the less the ionization of the proton donor This is mediated through the ommon ion effect, *i e* in an equilibrium reaction introduction of a product the reaction moves the reaction to the left

$$\text{Proton donor} = H^+ + \text{dissociated anion}$$

$$\text{Sodium salt of Proton donor} = Na^+ + \text{dissociated anion}$$

the body the chief buffers are H_2CO_3 and salts of H_2CO_3, HCO_3, $KHCO_3$, etc, H_3PO_4 and salts such as Na_2HPO_4, NaH_2PO_4, proteins in serum, in blood cells, and in other body tissues which weak proton donors at the pH of the body and therefore also Though there are other buffer systems in the body, these are

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P_{CO_2}	P_{CO_2}	P_{CO_2}
35 48	<35	>48
NORMAL RESPIRATORY EXCHANGE	RESPIRATORY ALKALOSIS (PRIMARY OR SECONDARY)	RESPIRATORY ACIDOSIS (PRIMARY OR SECONDARY)

FIG 17 1 RESPIRATORY REGULATION OF CO_2 AND HENCE OF H_2CO_3 CONCENTRATIONS IN BODY FLUIDS

Increasing the depth of inspiration increases the total alveolar volume and decreases the CO_2 concentration This permits diffusion of CO_2 from body fluids and results in a lowering of H_2CO_3 and hence of H^+ ion concentrations This type of pulmonary response is referred to as respiratory alkalosis It may occur as a primary change as in hysteria salicylate poisoning voluntary hyperpnea or develop secondary to a metabolic acidosis The reverse change i.e decreased respiratory excretion of CO_2 occurs in primary or secondary respiratory acidosis Numbers in Figure refer to mm Hg

the respiratory excursions can raise and lower the P_{CO_2} with concomitant increases and decreases in the amount of H_2CO_3 in the body fluids



$$P_{CO_2} \rightarrow CO_2 + H_2O \rightarrow H_2CO_3 \rightleftharpoons H^+ + HCO_3^- \qquad (5)$$

Hence, though the introduction of the strong proton donor (see formula 4) would be expected to increase the H^+ ion concentration by virtue of increases in H_2CO_3, decreasing the P_{CO_2} can and does readily restore the H^+ levels to normal This maintenance or regulation is mediated by alterations in respirations controlled by receptors and effectors sensitive to H^+ ion concentrations acting on the respiratory center Similarly, though the introduction of NaOH might be expected to deplete the H_2CO_3, retention of CO_2 by the above mechanism readily replenishes the supplies of this component of the buffer system

B In Pathologic States

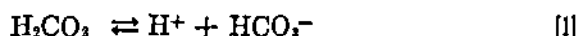
From the above discussion it can be seen that any interference with the normal pulmonary exchanges of CO_2 could alter hydrogen ion levels

1. Primary Respiratory Alkalosis—Compensated and Uncompensated Rapid deep breathing in excess of expiratory needs lowers the P_{CO_2} unduly and depletes the body of CO_2, H_2CO_3, and H^+ This can and oes happen with the overbreathing which occurs in hysteria, in cerebral sease states in hyperventilated respirator patients, in closed anaesthesia tems low in CO_2, and in the early phase of salicylate poisoning It can be produced by voluntary hyperventilation Such loss of CO_2 results

present in much lower concentrations and contribute less to the over all regulation of H^+ ion concentration

A The Carbonic Acid Bicarbonate Buffer System as a Prototype

The operation of the carbonic acid bicarbonate buffer system (see formulae [1] and [2]) following the introduction of compounds which in solution yield high concentrations of OH^- or H^+ ions is shown in formulae [3] and [4] illustrating the "common ion" effect *i e*, the presence of HCO_3^- from $NaHCO_3$ suppresses the *ionization of H_2CO_3 and thereby decreases the* H^+ ion concentration



$$H_2CO_3 \rightleftarrows H^+ + HCO_3^- \quad [1]$$



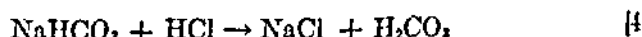
$$NaHCO_3 \rightleftarrows Na^+ + HCO_3^- \quad [2]$$

When NaOH is added to a system which contains the above buffer it reacts to yield $NaHCO_3$ and water



$$H_2CO_3 + NaOH \rightarrow NaHCO_3 + H_2O \quad [3]$$

This prevents the large excess of OH^- ions which would have resulted from the dissociation of NaOH With the introduction of HCl the following reaction occurs



$$NaHCO_3 + HCl \rightarrow NaCl + H_2CO_3 \quad [4]$$

In this way the large increment of H^+ ions which would have occurred from the addition of HCl is largely cancelled or replaced by a much smaller gain from the H_2CO_3 Similar simple equations can be written to illustrate the operation of the phosphate, protein, and other buffer systems

It is immediately apparent that the continued maintenance of a constant H^+ ion concentration demands an unlimited supply of buffer *This is* achieved by regeneration or replacement of the body buffers via the pulmonary and the renal regulatory mechanisms

II. The Role of Respiration in the Maintenance of Body H^+ Ion Concentration

A In Health

In keeping with Henry's law the quantity of H_2CO_3 in solution in the body fluids depends on the partial pressure of CO_2 (P_{CO_2}) in contact with body fluids via the pulmonary alveolar membrane The partial pressure of CO_2 varies in turn with the volume of the alveolar space These interrelations are shown in figure 17 1

It is readily apparent therefore that alterations in the depth and rate of

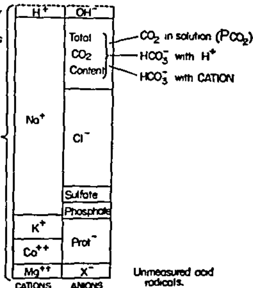
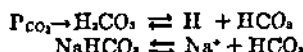


FIG 17 2 GAMBLE DIAGRAM OF THE ELECTROLYTES WHICH DETERMINE THE ANION-CATION BALANCE IN BODY FLUIDS

The chief cations (positively charged) are sodium potassium calcium and magnesium In previous usage these electrolytes were called fixed bases a term which is meaningless in the light of current definition of acids and bases The chief anions (acids in archaic terminology) are shown on the right chloride sulfate phosphate proteins and the undetermined or X fraction The relative excess of cations over anions or the relative deficiency of anions compared to cations determines the concentration of bicarbonate and ultimately the H ion level by the common ion effect



$$P_{CO_2} \rightarrow H_2CO_3 \rightleftarrows H + HCO_3$$
$$NaHCO_3 \leftrightarrows Na^+ + HCO_3$$

Decreases in bicarbonate as a result of increases in anion or decreases in cation in the Gamble diagram diminish the common ion effect and permit H_2CO_3 to ionize further and yield more H^+ ions This ionization decreases when the common ion effect is increased as by excesses of cation or deficiencies of anion

or with bicarbonate which is readily replaced from carbonic acid If the converse is true, *i e* if the chloride of the diet exceeds the sodium intake, the surplus of chloride appears in the urine in association with cations other than sodium or with the ammonium ion which the kidney can manufacture from glutamine in time of need In other words the kidneys can conserve fixed anions such as chloride and phosphate while excreting excesses of fixed cations such as sodium and potassium, and vice versa Similarly, they can within limits excrete any nonvolatile anions which may arise within

in a shift in H^+ ion levels to the alkaline side and is referred to as a primary respiratory alkalosis If the change in pH is minimal it is referred to as compensated The designation "uncompensated primary respiratory alkalosis would be reserved for those patients in whom definite changes in pH from the normal range of 7 35 to 7 45 to an abnormal value such as 7 5 or 7 6 occurred However the pH effects of such a respiratory alkalosis are minimized by the other buffer systems of the body and by renal adjustments which are discussed in section III

2 **Secondary Respiratory Alkalosis.** Comparable decreases in the P_{CO_2} can also occur secondary to disturbances in the hydrogen ion concentration in disease states Thus in diabetic acidosis and coma, the acidosis of far advanced renal failure, or the end stage of salicylate poisoning the decrease in pH results in hyperpnea or Kussmaul breathing in response to stimulation of the respiratory center This superimposes an element of secondary respiratory alkalosis upon the fundamental disturbance

3 **Primary Respiratory Acidosis.** Asphyxia, rebreathing of an atmosphere high in CO_2, and cardiopulmonary diseases can result in distinct *increases in the P_{CO_2} and H_2CO_3, i e in a primary respiratory acidosis* uncompensated or compensated depending on whether the H^+ ion concentration is or is not changed Again the buffer function as the first line of *defense in preventing such changes in pH and, as will be seen in section III* the kidneys also play an important role

4. **Secondary Respiratory Acidosis** Under conditions such as vomiting or *excessive administration of alkali the lowering of hydrogen ion concentrations results in a decreased expiration of CO_2* This superimposes a secondary compensatory respiratory acidosis upon the primary disturbance

III. The Role of the Kidneys in the Maintenance of H^+ Ion Concentration in the Body Primary Reactions

A In Health

The kidneys help maintain hydrogen ion levels constant by regulating the urinary output of exogenous and endogenous anions and cations In figure 17 2 the electrolyte composition of plasma is shown *in the form of* the traditional Gamble diagram and the bicarbonate portion of the carbonic acid buffer system has been marked In health the kidneys, as needed alter the excretion of anions and cations *so that the bicarbonate remains constant*

1. **The Excretion of Excesses of Fixed Cation or Anion** If the dietary *intake of sodium exceeds that of chloride, the* kidneys elaborate a urine which contains more sodium than chloride The excess of sodium ions is excreted in association with anions which may be available for excretion

renal losses of potassium in the production of deficiencies of this ion have been amply established (Is v) even though in the unstressed animal potassium conservation can be marked during periods of deprivation (Iw) In his original report Darrow *et al* (In) cited unpublished studies which indicated that low potassium diets unaccompanied by extra intake of sodium and chloride did not produce the marked lowering of muscle potassium the rises in cell sodium nor the hypochloremic alkalosis Since then other workers have shown that significant degrees of potassium depletion *i.e* five per cent of the body stores may be induced without production of either hypochloremia or alkalosis (Ix y) However data are too limited at present to assert that hypochloremic alkalosis associated with potassium losses always represents chloride deficiency or necessitates sodium loading

IV The Role of the Kidneys in the Maintenance of H^+ Ion Concentration in the Body Secondary Reactions

It will be recalled from earlier discussions that renal reactions were stated to accompany acute primary respiratory disturbances In the case of respiratory alkalosis these consist of the excretion of a urine low in H^+ and high in K^+, Na^+ and HCO_3^- This stems from the fact that with the decrease in P_{CO_2} less H_2CO_3 is formed and less H^+ ions are available for competition with K^+ in the cation exchange process known to occur during the reabsorption of filtered sodium This greater output of sodium and potassium will tend to lower bicarbonate and restore the bicarbonate carbonic acid ratio to normal Urine bicarbonate also increases presumably because with a deficiency of H^+ ions less H_2CO_3 is formed from filtered HCO_3^- and reabsorbed back into the body as H_2O and CO_2

In the case of acute primary CO_2 retention the immediate response is the elaboration of a more acid urine containing less bicarbonate sodium potassium and more Cl^- and NH_4^+ Thus retention of cations permits an expansion of bicarbonate which tends to return the bicarbonate carbonic acid ratio to normal Chronic primary CO_2 retention ultimately results in a lowering of the serum chloride levels *i e* an establishment of a new steady state of hypochloremia which allows a further increase in the bicarbonate levels of body fluids This might be looked upon as a secondary metabolic alkalosis which serves to shift H^+ ion concentrations back toward normal

V The Participation of Tissues in H^+ Ion Homeostasis

In acute primary respiratory alkalosis the losses of CO_2 via the lungs and of Na^+ and K^+ ions in urine are accompanied by transfers of H^+ and K^+ ions out of cells and an entry of Na^+ into cells In acute primary respiratory acidosis the reverse occurs *i e* as an increased excretion of H^+ ion

the body, such as beta hydroxybutyric and aceto acetic, in company with H^+, NH_4^+ or other cations

B In Disease States

1. Metabolic Acidosis The ability of the kidney to adjust the output of anions and cations and maintain bicarbonate and H^+ constant may be overwhelmed by increased loading diminished renal function or both Thus, an intake of foreign nonmetabolizable anions such as those of salicylic or boric acid or an accumulation of aceto acetic or beta hydroxybutyric acids as in unregulated diabetes, in excess of the renal excretory capacity will result in an accumulation of these anions in body fluids with displacement of the bicarbonate ion This is termed metabolic acidosis due to absolute excesses of anion Under these circumstances the common ion effect which minimizes the ionization of H_2CO_3 is diminished and the H^+ ion level increases The respiratory center is stimulated and respirations increase culminating in Kussmaul breathing in the advanced cases This lowers the P_{CO_2} and produces a secondary compensatory respiratory alkalosis

Metabolic acidosis may also result from excessive losses of a fixed cation and of sodium in particular, as in diarrhea In terms of the Gamble diagram such cation deficits represent relative excesses of anions and again a metabolic acidosis results

2 Metabolic alkalosis A deficiency of fixed anions such as that present in hypochloremia secondary to losses of chloride during vomiting or gastrointestinal lavage or as a result of excessive mercurial therapy evokes an expansion of the bicarbonate level The common ion effect suppresses the ionization of H_2CO_3 and the H^+ ion concentration decreases This represents primary metabolic alkalosis as a consequence of an absolute deficit of fixed anion *i e* chloride A similar change in bicarbonate and in H^+ ion can be seen with an excess of sodium ions produced by the administration of sodium with a metabolizable anion, such as lactate This results of course in a relative deficit of fixed anion Irrespective of the origins the development of a metabolic alkalosis with pH changes leads to a secondary respiratory acidosis, *i e* the shallow respiratory movements of the alkalotic patients permit an accumulation of CO_2 and a rise in P_{CO_2}

The hypochloremic form of metabolic alkalosis may also reflect as Heppel first suggested (1m), a depletion of cellular potassium Insofar as this category is concerned Darrow *et al* (1n-r) have presented evidence that as potassium moves out of cells, sodium and hydrogen move in An intracellular acidosis and an extracellular alkalosis results Under these circumstances the lowering of chloride has been interpreted as originating from dilution of chloride space, from extracellular transfers or segregation of chloride, or most likely from losses in urine The importance of continued

VI. The Range of Anion-Cation Values in Ambulatory Hospitalized Children Not in Keto-Acidosis (Serum Total CO_2 Content of 20 mEq. Per Liter or Higher)

The effectiveness of the homeostatic mechanisms operative in the maintenance of body fluid composition is readily evident from the relative constancy and narrow range of distribution of serum levels of electrolytes in healthy nondiabetic children. How do these values compare with those obtained in a group of ambulatory, hospitalized diabetic children under diet and insulin therapy?

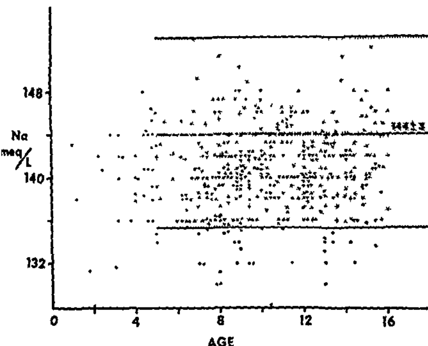


FIG 17-4 SERUM SODIUM VALUES IN DIABETIC CHILDREN WITH TOTAL CO_2 OF 20 MEQ OR MORE PER LITER

Legend as in figure 17-3. The comments on chloride, i.e. the presence of values below the usual range of variation in nondiabetics apply equally to sodium (2c). In current thinking this relative hyponatremia (and the relative hypochloremia as well) may represent depletion, chronic hypo-osmolarity, dilution, excess of lipids or a new steady state (2b).

takes place in urine with accompanying decreases in the output of potassium, while hydrogen and potassium ions enter the cells and sodium moves out

Similarly, in primary metabolic alkalosis, such as that resulting from losses of chloride in vomitus, sodium enters cells as potassium ions move out of cells, in primary metabolic acidosis, as in diabetic coma, the reverse of these movements occurs, *i e* sodium leaves cells while potassium goes in

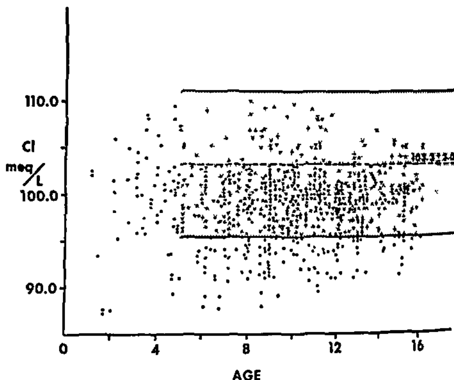


Fig 17-3 Serum Chloride Concentrations in Ambulatory but Hospitalized Juvenile Diabetics When Serum Total CO_2 Content was 20 mEq per Liter or Higher

The dividing line between adequately regulated and therefore nonketotic non acidotic diabetics has been taken at 20 mEq per liter because values as low as this are encountered in healthy nondiabetic children (2a) The dotted line indicates the mean value of the serum chloride concentrations in such a control series of healthy nondiabetic control subjects (5 to 18 years of age) from a well run home for children The shading above and below the mean extends three standard deviations A number of the diabetic children have unduly low chloride levels as indicated by the scatter of values below the minus three standard deviations range (2c) See next figure for possible explanations of this relative hypochloremia

A Serum Electrolyte Patterns in Controlled Diabetics

Figures 17-3 through 17-7 show serum chloride, sodium, potassium, calcium, phosphorus, total protein, albumin, and globulin values in [illegible]

[illegible] established in healthy nondiabetic children, *some of the values* are more than three standard deviations removed from the mean This is especially true of the low chloride and sodium values which suggest that some of the diabetics may be salt depleted, though alternative possibilities such as chronic hypo osmolarity, excesses of water, hyperlipemic effect, and new steady states have to be considered The interpretation of hyponatremia in general has been discussed by the author elsewhere (2a, b) In these diabetics salt depletion, on the basis of osmotic diuresis due to glycosuria and possibly a slight hyperlipemic effect appear to be the most likely explanations The tendency to elevations of the serum cholesterol levels (figure 17 8) provide some support for the latter

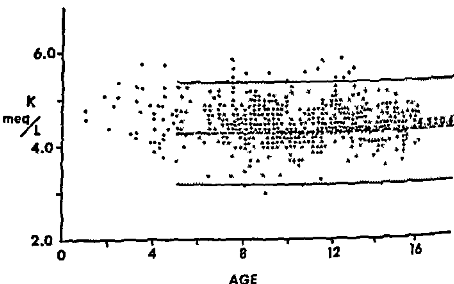


FIG 17-5 THE RANGE OF SERUM POTASSIUM LEVELS IN NONKETOTIC NONACIDOTIC JUVENILE DIABETICS I E WITH TOTAL CO_2 OF 20 MEQ OR MORE PER LITER

Though the potassium concentrations in fasting diabetic children match the control values rather closely (2c), there are a number of patients who fall above the usual range in the nondiabetic controls The dotted line refers to the mean value and the shading indicates ± three standard deviations from the mean (2a)

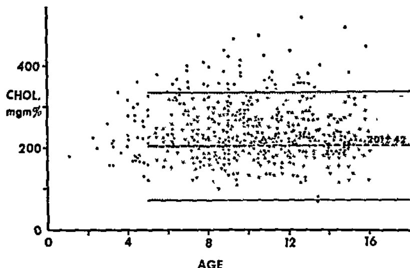


FIG 17-8 SERUM CHOLESTEROL VALUES IN NONKETOTIC NONACIDOTIC DIABETIC CHILDREN

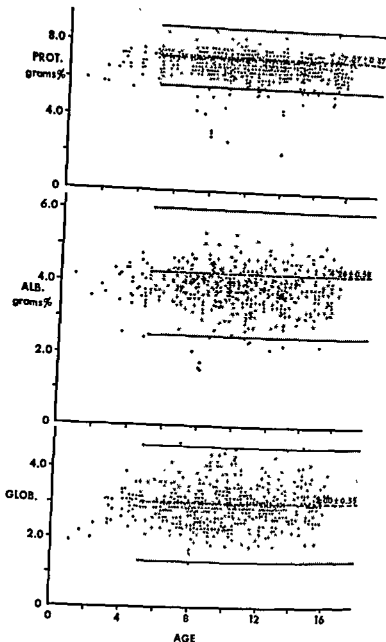
The traditional hypercholesterolemia of diabetics is evident in some of these children in whom regulation was satisfactory as indicated by undiminished serum total CO_2 levels Dotted line and shaded area again indicate mean ±3 S D in nondiabetic controls (2c)

olism, dehydration, deglycogenation, and negative balances of cell nitrogen

Summary

The maintenance of H^+ ion concentrations in the normal range in diabetics and nondiabetics is dependent upon buffer systems and ultimately upon renal and respiratory regulation Thus concentrations of the carbonic acid-bicarbonate buffer components are determined by respiratory regulation of CO_2 excretion and the renal output of cations and anions Other buffers such as the proteins and the phosphates, electrolyte transfers between cells and extracellular fluids, and the osmotic activities of electrolytes within cells also participate in the maintenance of H^+ ion levels

In the diabetic in whom insulin supplies fall below the levels necessary for maintaining carbohydrate utilization within usual limits the body shifts to fat for energy purposes The beta oxidation of fatty acids produces acetyl CoA in excess of the ability of the tissues to utilize this derivative The excesses of acetyl CoA are converted to beta hydroxybutyric and acetoacetic acids and to acetone. The first two products function as anions and ultimately displace bicarbonate. This decreases the common ion effect of



17-7. SERUM TOTAL PROTEIN, ALBUMIN, AND GLOBULIN LEVELS IN CONTROLLED DIABETICS

e total protein and albumin levels are reduced in some diabetics (values below l area representing range of normal). Globulin concentrations are unchanged

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bicarbonate upon the ionization of H_2CO_3 and H^+ increases, *i e* a metabolic acidosis develops Renal failure as a consequence of dehydration and salt depletion accentuates this further The respiratory adjustment (increased ventilatory loss of CO_2) tends to restore the H^+ ion to normal levels by *virtue of a secondary respiratory alkalosis.* As the disturbance progresses Kussmaul overbreathing eventually sets in

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PART III

DEVELOPMENTAL ASPECTS AND COMPLICATIONS

CHAPTER 18

Diabetic Acidosis and Coma in Adults and Children: Precipitating Causes, Presenting Symptoms and Signs, Mortality, and Controversial Aspects of Therapy

While there can be no doubt that the phrase diabetic acidosis and coma" refers to the clinical and biochemical changes which occur in a diabetic following upon a major loss of carbohydrate tolerance, published reports (1a–q 2a–n 3a–x) often use the term loosely without precise quantitative significance Thus acidosis has been variously interpreted to indicate that the serum total CO_2 content or combining power is reduced to 20 volumes per cent (1a n) 29 volumes per cent (3g), or some value intermediate between these two (3r) The higher limits have been used by workers who encountered a significant mortality in such patients (3g, h) In other clinics the appearance of overbreathing of the Kussmaul type has been employed as an index of acidosis This usually develops when the total CO_2 content is reduced to approximately 20 or 22 volumes per cent, but again the relationship is somewhat variable Patients who are not overbreathing but who have ketone bodies in urine and blood increased above levels characteristic of controlled diabetics or healthy nondiabetics, associated with total CO_2 values higher than the limit set for acidosis are said to have diabetic ketosis The combination phrase keto acidosis has been used to refer to patients in this group who are on the verge of acidosis Similarly though it has been urged that the term diabetic coma be reserved for the totally unconscious or the markedly stuporous patient, in some publications the words acidosis and coma are still used interchangeably It has therefore been suggested that the patients who develop acidosis but remain conscious be classified as diabetic precoma (3i)

To provide objective standards for comparison we divide our cases in accord with the serum total CO_2 content at the time of admission Values between 15 1 and 20 0 mEq per liter are classified as ketosis The term acidosis is reserved for patients with a serum total CO_2 content below 15 0 mEq per liter For purposes of comparison we further subdivide these into the 0–10 and 10 1–15 0 mEq categories Members of either of these two groups who are unconscious and unresponsive are said to be in coma

coma The incidence has been expressed in terms of the index described above, i e, the number of admissions for acidosis or coma in relation to the duration of the diabetes has been found to be one attack of acidosis or coma per 58 patient months of diabetes In keeping with the data on adults, in our group there is a slightly greater number of girls but the mortality rates in our series and those of others seem to be the same in the two sexes However the total numbers of deaths in any particular series are small Owen's suggestion (31) that adolescence is associated with a higher frequency of coma is not borne out by our statistics, since on a percentage basis the rates are identical in the 8–12- and 12–16 year-old groups *(figure 18-1)*

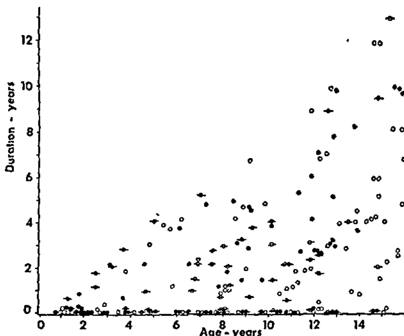


FIG 18-1 OCCURRENCE OF ACIDOSIS AND COMA IN RELATIONSHIP TO AGE AND TO DURATION OF DIABETES

Open circles represent girls closed circles represent boys admitted with serum total CO_2 content of 10 mEq per liter or less Cross bar identifies patients admitted with CO_2 content of 10 1 to 15 mEq per liter Coma occurred more often in girls than in boys *It was more frequent during the first year of diabetes but it must be noted that* in a high percentage of our patients diagnosis of diabetes was first made during an admission in coma or acidosis The numbers of cases in the 8–12 and the 12–16-year-old group are about the same

I. *Incidence of Diabetic Acidosis or Coma*

There are no satisfactory data from which the actual frequency of diabetic coma can be estimated The mortality statistics from various clinics provide only fragmentary information on this point, since they *are usually not related to the total diabetic population* Likewise, the proportion of diabetic coma in the diabetic and nondiabetic population of a hospital is without meaning because *the sample is not quantitated* and the custom of optional admissions for instruction, regulation etc varies Rabinowitch (3y) has quoted a figure of 1 3500 as the coma rate without reference to time intervals, in a year's sample of the Joslin series coma accounted for 1 5 per cent of the admissions (3z), in Dillon and Dyer's group (3g) this rate was 11 2 per cent It would be desirable therefore, to relate the frequency of acidosis and coma to the total diabetic *load in a particular clinic and perhaps express it, as we have done with our* juvenile diabetics in the form of an acidosis or coma index, i e , the average number of admissions for this complication per month or year of diabetes For purposes of generalization and comparison with the experiences of others this figure could then be standardized, i e , corrected for variations in the age and sex of a particular population from national prevalence estimates and for factors known to influence the frequency of coma i e *the age of the patient, the duration and severity of the diabetes, the eco*nomic status etc The importance of such variables in determining the *mortality in diabetic coma has been recognized* (3h–m u) (see section IV), but these principles have not been applied to the studies of the frequency of diabetic coma Without such standardization evaluation of the efficacy of particular treatment regimens is not feasible

A *Children's Hospital of Pittsburgh Data on the Frequency of Diabetic Acidosis or Coma in Children*

In the available compilations of statistics on acidosis and coma without particular reference to age groups this complication is reported to occur with greatest *frequency during the first year following* the onset of diabetes (1d) It has been concluded that, in terms of total numbers of adult patients, females outnumber *males and usually show* a higher mortality rate (1c, e g, 3g, i, l) Younger patients develop this complication more often than do the adults (1d, g, h, 3b, f, i, l, n, x)

We have reviewed our Pittsburgh series (1o) of 191 episodes *of acidosis* and coma in children up to the age of 16 years and found that, as in the adult or mixed series, *the highest frequency is recorded* during the first year following the recognition of diabetes (figure 18-1), chiefly because such a large proportion of the patients are first diagnosed in acidosis or

TABLE 18 1

Precipitating causes and presenting symptoms and signs in diabetic acidosis or coma

Series	Years	Number	Children %	Etiology (% of Patients)			Symptoms and Signs (% of Patients)						
				Undiagnosed Diabetes	Inadequate Rx	Infections	Vomit	Abdominal Pain	Leukocytosis	Stupor	Coma	Blood Pressure Decreased	Anuria
Joslin (1d)	1923–1932	221	74							16	16	2	
Joslin (1g)	1923–1936	318	42	2	5	2							
Joslin (1h)	1910–1942	525	†	10	53	23							
Marble (1f)	1935	55		22	58	20						11	
Beardwood and Rouse (3p)	1941	220	36	20	11	26	54				42		
Baker (3f)	1923–1934	108	26	12	37	30	67	41	55	38	30	Yes	
Rabinowitch (3h)	1939	125									20		
Dillon and Dyer (3g)	1937	268	25	36		34			92		30		
Owens (3i)	1939	92	79								53		
Zieve (3u)	1953	124		17		16	64		16,000*		27	19	8
Harwood (3t)	1945	35	48							8	26		
Harwood (3t)	1945–1951	67	24	19	73	44				18	16		
Collen (3l)	1930–1940	315	24	5	22	54	8			30	44	18	
Hagtvet (3n)	1932–1941	62	32	24	51	38				29	18	4	
Foster (3o)	1939	82	4		42	40						33	
Rodriguez (3x)	1918–1954	123	15	66									
Danowski (3q)	1925–1945	188	11	13	32	56	71		22,100*		24	32	
Danowski (1o)	1948–1955	191	100	31	42	61	79	39		37	8		

* Per mm³

† 234/525 in 0–20 year age group

II. Seasonal Incidence and Precipitating Causes of Acidosis and Coma

A In Adult and in Mixed Series

The records of the Mayo Clinic (3f) and those of Joslin's group (1c, d) indicate that, contrary to expectation, acidosis and coma are more frequent during the summer than the winter It has been suggested that departure from diabetic regulation in the course of vacation periods is responsible for this greater incidence during a time of the year when respiratory and related infections are at a minimum The data of Collen (3l) differ in that coma was more frequent in the winter In the Pittsburgh series of pediatric patients, acidosis and coma occurred most often during the months of June and October (figure 18-2)

1. Inadequate Diet and Insulin and the Role of Emotional Factors Published reports of acidosis and coma in children and adults from the above groups of patients and from other clinics (see table 18 I) agree *that absence of adequate diabetic regulation, as in previously undiagnosed* diabetes or in those who do not follow prescribed regimens, is the commonest precipitating cause However the work of Mirsky (4a) and the success of free or liberal dietary regimens (4b–e) (see also Chapter 15) indicate that increases in the intake of food *per se* cannot be expected to precipitate acidosis or coma The studies of Hinkle (4f–h) (see Chapter 22), of Rosen and Lidz (4i), and of others (4j) show that dietary trans-

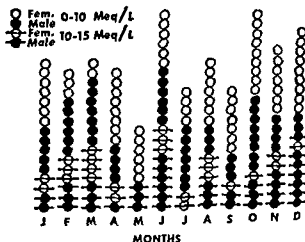


FIG 18 2 ACIDOSIS AND COMA IN RELATIONSHIP TO THE MONTH OF THE YEAR

The 0-10 and 10 1–15 mEq per liter refers to serum total CO_2 content prior to therapy There is no clear cut separation though this complication did occur more often during June and October and least often during the month of May

acidosis and coma However enough isolated instances have been found to indicate that an emotional conflict can mark the beginning of inadequate dietary and insulin regulation With more detailed attention to this factor we have found during the past year that some 10 to 20 per cent of the admissions are preceded by periods of emotional turmoil at home or in school (41)

The possible role of intrinsic gastrointestinal disease of unknown etiology in producing nausea and vomiting and interfering with food intake must be cited Routine roentgenographic examinations of the gastrointestinal tract of diabetic patients not admitted for acidosis or coma have shown an unexpectedly high incidence of duodenal deformities and craters It may be therefore that some cases of coma begin with intrinsic gastrointestinal disease These findings are discussed in Chapter 24

III Presenting Symptoms and Signs in Adults and Children

1 *Clinical History and Physical Findings*

Overbreathing is of course one of the most frequent clinical manifestations of acidosis or coma In our group of children the incidence was 73 and 24 per cent in the groups admitted with serum total CO_2 content of 0 to 10 and 10 1 to 15 mEq per liter respectively (1o) As indicated earlier tachypnea is a more frequent finding than overbreathing occurring in virtually all of the patients with serum total CO content reduced below 10 mEq per liter and in one third of these in the 10 1 to 15 mEq group It is apparent from the above figures however that the lower the CO_2 content the greater the incidence of tachypnea and of Kussmaul breathing

The recorded incidence of vomiting varies up to 79 per cent in the adult and mixed series (table 18 I) in our pediatric population (1o) this symptom was present in three quarters or more of the children

Abdominal pain may be a concomitant or a sequel of the nausea and vomiting occurring in 40 per cent or more of the patients in the published series (3f) and recorded in two fifths of our children As has been often pointed out this symptom may be intense enough to mimic intrinsic abdominal disease (4m n)

The frequency of frank coma varies from 16 to 55 per cent in the published reports (table 18 I) Since loss of consciousness is more apt to occur in the cases of prolonged acidosis (3h m q u) the incidence is higher in the wards of general hospitals than in private clinics Drowsiness or stupor is present somewhat less often than is coma 8 to 38 per cent of the patients in the published series a range of values in keeping with the findings in our juvenile series

It has been repeatedly pointed out that circulatory collapse as a consequence of dehydration and salt depletion may be present at or shortly

gressions are frequent manifestations of underlying emotional disturbances and the loss of carbohydrate tolerance is to be attributed to these rather than to the increased food intake *per se* The failure to provide enough additional insulin then results in inadequate diabetic regulation

2 Infections as Precipitating Cause of Acidosis and Coma Published reports are in agreement that major or minor infections used to rank with inadeqate therapy as one of the common precursors of diabetic acidosis or coma (table 18 I) In essence this is another example of inadequate therapy, *i e*, insufficient insulin is provided to meet the increase in requirements which so frequently occurs in infections It is to be expected that as data gathered during the era following introduction of effective chemotherapeutic and antibiotic agents accumulate the bacterial infections will play a lesser role in precipitating coma

3 Hypoglycemia as a Precursor of Keto Acidosis and Coma It is probable that insufficient attention has been paid to the loss of carbohydrate tolerance which follows inadvertent insulin hypoglycemia If not met by adjustments in diet and insulin dosage, a deterioration of diabetic regulation which may result in acidosis and coma occurs This has been emphasized in the series published by Danowski, Winkler, and Peters (3q) It may be presumed that in other reported series such cases were included among the inadequately regulated and were therefore lost as a group

4 Miscellaneous Antecedents of Acidosis and Coma The published reports include factors such as pregnancy, surgical operations (4k) and thyroid crises (1g) as occasional precipitants of acidosis and coma Though in any particular group of such diabetic patients coma may occur with high frequency, they contribute only a small sum to the total problem of diabetic acidosis and coma

B In the Children s Hospital of Pittsburgh Series of Juvenile Diabetics

Table 18 I includes a summary of the antecedent and therefore the probable causes of diabetic acidosis and coma in our series of diabetics Inadequate regulation especially if one includes the large proportion of previously undiagnosed patients is the chief origin of this complication in juvenile and adult diabetes Respiratory and other infections are next in frequency Insulin shock marking the onset of the loss of carbohydrate tolerance and culminating in acidosis was recognized in only a few patients Miscellaneous precursors included dental extractions vaccinations and inoculations In a few instances no specific precipitating factor could be identified

It is difficult at this time to extract from published records or from our own the probable contribution of emotional disturbances in precipitating

glomerular filtration rate either on the basis of circulatory collapse (1a, b, d, f, 3g, h, l, n, o, q, r, t), acute tubular damage (6a–d), or chronic vascular disease as in the Kimmelstiel-Wilson syndrome (see Chapter 23) It has also been recognized that albuminuria and transient increases in the formed elements of the urine frequently appear in urines obtained during diabetic acidosis and coma Presumably these result in the main from some unidentified and reversible alterations of filtration and reabsorption perhaps representing a mild form of the acute tubular damage or lower nephron nephrosis referred to above

2. Formed Elements of the Blood. A polymorphonuclear leukocytosis is a frequent finding, resulting in part from dehydration and largely from the increased adrenocortical activity demonstrated in clinical and experimental studies of acidosis and coma (7a–g) This is attended by lymphopenia and eosinopenia The usual rise in the erythrocyte count and in the relative blood cell volume or hematocrit is largely a reflection of vascular, extracellular, and cellular dehydration

3. Blood and Serum Solutes. *a Hyperglycemia* is of course the *sine qua non* of diabetic acidosis and coma, resulting from a combination of

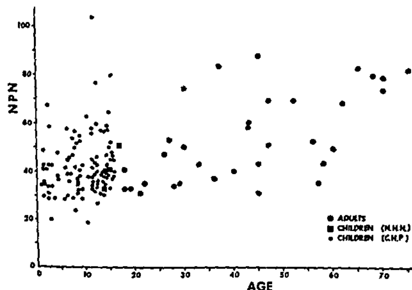


FIG 18-4 AZOTEMIA IN UNTREATED ACIDOSIS OR COMA

The majority of the older diabetics (large circles) and a lesser proportion of the juveniles (small circles and squares) were azotemic on admission in acidosis or coma (3q 1o) in which serum total CO_2 content was 10 mEq or lower

following upon admission (1a, b, d, f, 3h, l, n, o, q, r, t) In the published series this occurred in as high as 60 per cent of the patients (3n), but was only rarely present in our pediatric group Finally, it should be pointed out that weakness, paralyses, or paraesthesia as possible manifestations of potassium depletion are extremely difficult to evaluate in acidosis or coma patients because of the nonspecific prostration but should be mentioned as possible important presenting symptoms

B Laboratory Findings

1. Urine Analyses. Examination of the urine on admission will almost invariably show glycosuria and ketonuria to be present In some patients however, the urine does not reflect the degree of glycemia and ketonemia. These represent instances of chronic or acute renal insufficiency which may be present despite the excretion of large volumes of urine This observation has been reported many times (5a–k), though it is not very frequent in *the experience of any particular clinic* The discrepancy between blood and urine levels of sugar and ketone bodies arises from decreases in the

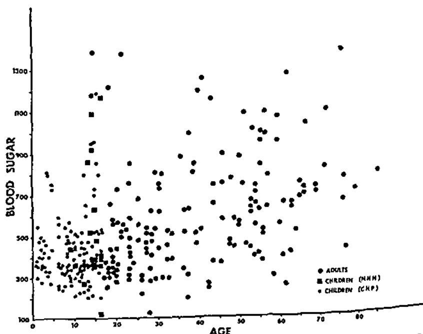


Fig 18-3 Admission Blood Sugar Levels in Diabetic Acidosis and Coma Characterized by Serum Total CO_2 Content of 10 mEq per Liter or Less

Blood sugar levels in adults (large circles) were higher on the whole than those in juvenile diabetics (squares and small circles (3q 1o))

glomerular filtration rate either on the basis of circulatory collapse (1a, b, d, f, 3g, h, l, n, o, q, r, t), acute tubular damage (6a–d), or chronic vascular disease as in the Kimmelstiel-Wilson syndrome (see Chapter

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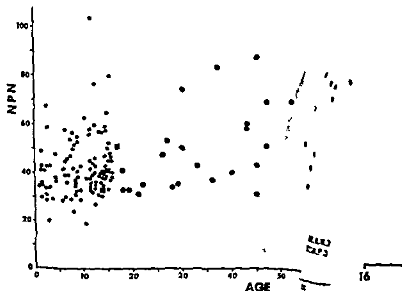


Fig 18-4 Azotemia in Untreated Acidosis

The majority of the older diabetics (large circles) and … AND juveniles (small circles and squares) were azotemic on adm… (3q lo) in which serum total CO_2 content was 10 mEq … lower … or

a progressive decrease in carbohydrate utilization and rising gluconeogenesis It may attain levels approximating 2000 mg per cent (8a–c) the more usual concentrations *range between 400 and 800 mg per cent* and values as low as 150 mg per cent are compatible with the diagnosis of acidosis and coma Figure 18 3 shows admission blood sugar values in a group of adult and juvenile diabetic acidosis and coma patients under the care of the author and his colleagues (1o 3q) *It is evident that* acidosis or coma can occur with blood sugar values only slightly above the normoglycemic range, but the combination of acidosis hyperpnea and normal or slightly elevated blood sugar levels should raise the question of alternative possibilities, *i e* salicylate or boric acid poisoning (8d) or far advanced renal failure

b Azotemia is a frequent finding in the severely ill patient showing

phase the whole blood nonprotein nitrogen, whether previously elevated or not often falls below ordinary fasting levels

c The serum total CO_2 content or combining power is invariably reduced in acidosis and coma As pointed out earlier this is a metabolic acidosis resulting from an accumulation of ketone bodies and losses of further gree nor

with the patient's chances of recovery (3g–i, m n–w) It is true however that when the total CO_2 content is greatly reduced hyperpnea is invariably

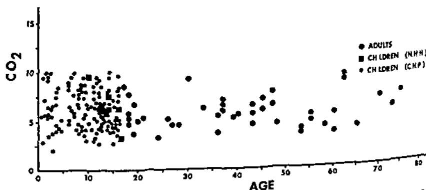
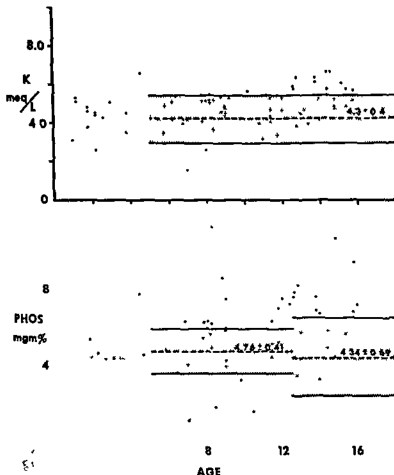


Fig 18-5 Serum Total CO_2 Content in Adult and Juvenile Diabetic Acidosis and Coma in the 10 mEq per Liter or Lower Series

Large circles identify adults in the previous series reported by the author and his colleagues (3q) The small circles and squares represent juvenile diabetics (1o 19)

dration (9b) and the remainder to altered transport and metabolism of lipoproteins (9c)

h Serum calcium was increased in one half of the patients in our series (10) in whom measurements were made prior to therapy (figure 18-11)



PHOSPHORUS LEVELS PRIOR TO THERAPY OF ...SIS OR COMA IN CHILDREN

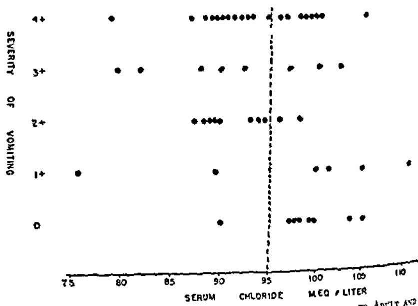
...mia and hyperphosphatemia in diabetic acido-...m potassium and phosphorus concentrations ...range of normal in healthy children (shaded ...9)

d Serum sodium and chloride values were low in only some of these patients when they first entered the hospital (figure 18 6) even though repletion studies indicate that all develop deficits of these electrolytes during acidosis and coma as a consequence of losses in vomitus and in urine (1o) Figure 18-7 shows a correlation between the intensity of vomiting and the degree of hypochloremia (3q)

e Extracellular potassium and inorganic phosphorus levels may be elevated, normal, or low (figure 18 8) depending upon a) the relative proportions of the external losses of water and potassium or phosphorus and b) the rate at which potassium or phosphorus is transferred from cells to the extracellular fluids The higher values are usually encountered in the more seriously ill patients and especially in those who develop anuria (1o)

f Serum total protein albumin, and globulin concentrations show no change (figure 18 9) The total plasma content of these constituents is actually decreased however, because plasma volumes are contracted as a consequence of the salt depletion and dehydration

g Serum cholesterol values tend to be elevated but may fall within the normal range (figure 18 10) Part of the rise is attributable to dehy



F

prolonged vomiting

dration (9b) and the remainder to altered transport and metabolism of lipoproteins (9c).

h Serum calcium was increased in one-half of the patients in our series (1o) in whom measurements were made prior to therapy (figure 18-11)

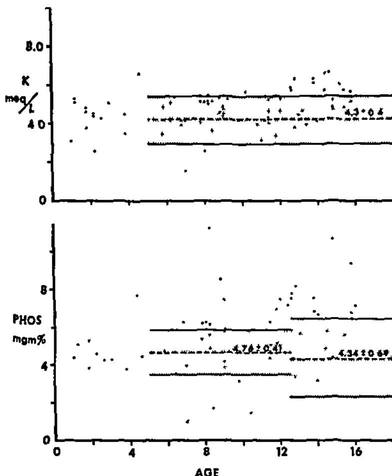


FIG 18-8 SERUM POTASSIUM AND PHOSPHORUS LEVELS PRIOR TO THERAPY OF DIABETIC ACIDOSIS OR COMA IN CHILDREN

In contrast to the frequent hyperkalemia and hyperphosphatemia in diabetic acidosis or coma of adults the pretreatment serum potassium and phosphorus concentrations may be virtually unchanged or below the range of normal in healthy children (shaded area depicts mean values ±3 S.D.) (1o 19)

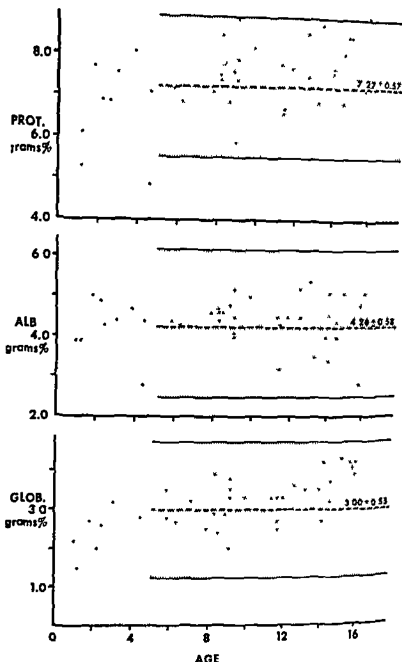


Fig 18 9 Serum Total Protein, Albumin, and Globulin Concentrations in Juvenile Diabetics in Acidosis or Coma

In each of these children the serum total CO concentration was 10 mEq per ... were comparable ... sses the mean ... er because ... ion and

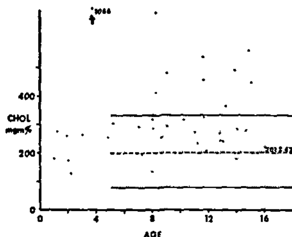


Fig 18-10 Cholesterol Levels in Diabetic Acidosis or Coma Children with Serum Total CO Levels of 10 mEq per Liter or Less

The hypercholesterolemia of unregulated diabetes was recorded in only some of the patients though acidosis or coma was present in all (10) The shaded area encompasses 99 per cent (mean ±3 S D) of the values in a group of healthy nondiabetic children (20)

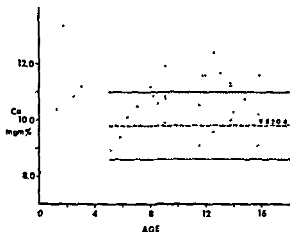


Fig 18-11 Serum Calcium Values Prior to Therapy of Children in Diabetic Acidosis or Coma

Shaded background indicates mean ±3 S D in nondiabetic control subjects

i Serum magnesium levels are usually elevated (10a–c) coexistent with deficits of this ion

There is no doubt that the composition of body fluids and the stores and distribution of many other body constituents, such as the trace elements and the vitamins, are also altered in coma even though data on these points are not available

IV. Mortality in Diabetic Coma

Review of the reports of various workers (see table 18 II) indicates that acidosis and coma do occur more frequently in the younger patients and therefore in those with the more severe forms of diabetes The mortality is highest in the older age group, especially among women, though as mentioned earlier Collen differs on this last point (3l, m) The importance of economic, biologic, biochemical and other variables upon the mortality has been stressed in a number of reports Thus in the Rabinowitch series (3h) factors such as the age, duration of the diabetes and the coma the degree of unconsciousness, the presence of associated disease, infection, hypotension, decreased total CO_2 content, and increased blood urea nitrogen levels were taken into account In keeping with the consensus Rabinowitch demonstrated that the mortality was directly related to age, unconsciousness, circulatory collapse, and the presence of other diseases a similar relationship was noted in the fatality rate and the degree of hyperglycemia and azotemia, but not in the total CO_2 content Rabinowitch's findings are in essential agreement with those of Dillon and Dyer (3g), Owens (3i), Baker (3f), Collen (3l), Beardwood (3p), Danowski (3q), Zieve (3u), and their co-workers

A Fatalities in Coma in Relationship to All Diabetic Deaths

In the days prior to insulin Joslin noted that during the period extending from 1898–1914, 64 per cent of all diabetic deaths occurred in coma (3z 1l) This decreased to 42 per cent during the era of therapy of undernutrition With the availability of insulin the Joslin group has recorded a progressive decrease in deaths attributable to coma, reaching the new low figure of one per cent of all diabetic deaths for the year *1953 (1m)*

B Mortality in Reported Series of Acidosis and Coma Patients

It is generally recognized that comparison of mortality statistics on diabetic acidosis and coma is difficult and probably impossible because of the great variations in the make-up of the acidosis and coma population in respect to the factors cited above Prior to the discovery of insulin the mortality from diabetic coma was virtually 100 per cent The data from the Joslin clinic (1m, n) illustrate clearly the reduction in the per

TABLE 18 II

Mortality in diabetic coma (mixed adult and pediatric series)

Series	Years	Number	Age	Sex M/F	Mortality %
Dunlop (3c)	1922 1931	45			60
Bertram (3d)	1923 1931	1007			20
Bertram (3e)	1923 1931	186			33
Baker (3f)	1923–1934	82	31 2	44/56	16
Dillon and Dyer (3g)	1937	268	37 8	81/187	44
Rabinowitch (3h)	1939	125		26/125	26
Owens and Rockwern (3i)	1936	92		28/64	51
Collen (3l)	1942	315		38/62	33
Hagtvet (3n)	1932 1941	62		30/32	15
Foster (3o)	1924–1939	82		35/47	17 1
Beardwood and Rouse (3p)	1935–1941	220			23 6
Danowski *et al* (3q)	1926–1945	188		73/115	18 1
Black and Malins (3s)	1943–1948	170			20 0
Harwood (3t)	1942–1944	35	41 8		20
Harwood (3t)	1944 1950	67	36	49/51	1 5
Zieve (3u)	1930–1948	124	36 6		29
Rodriguez and Casarin (3v)	1948–1954	128			17 2
Gronberg (1q)	1956	72		26/46	
Joslin I *et al* (1m, n)	1923–1931	179	30 9		15
Joslin II (1m, n)	1931–1940	284	29 1		10
Joslin III (1m n)	1940–1946	189	27 0		3
Joslin IV (1m, n)	1946 1951	154	31 1		3
Allen and Sherrill (2a)		9			55
Banting and Campbell (2b)		16			49
Burn and Schwab (2c)		6			33
Bock, Field and Adair (2d)	1923	7			28
Bunce (2e)	1927	3			0
Campbell (2f)		14			14
Chabanier (2g)	1927	28			32
Elias (2h)	1912–1913	25			52
Elias (2i)	1924 1925	42			24
Foster (2j)	1925	20			10
Foster (2k)	1923	15			46
Petrén (2l)	1927	57			14
Samson and Blatherwick (2m)		5			40
Strauss (2n)	1927	6			33
John (3a)	1929	71			6
Bowen and Hekimian (3b)	1923–1929	81		18/45	12 3

centage of such fatalities which followed the introduction of insulin in the eight years between 1923 and 1931 the mortality rate averaged 15 per cent, decreased to ten per cent in the next decade, and in the subsequent 11 years ending 1951 reached the new low of three per cent The over-all

F Gastric Intubation

Gastric intubation is a routine practice in some clinics (31-k) The author has had no direct experience with this in either the adult or the pediatric cases In both of his groups vomiting following admission and aspiration pneumonia have presented no problem and the author is therefore inclined to omit gastric aspiration especially since inadvertent passage of the tube into a bronchus and interference with the more important aspects of coma therapy may occur

Summary

The actual incidence of diabetic acidosis and coma is in doubt since it is not customary to relate their occurrence to the duration of diabetes Insufficient insulin is the ultimate cause of all diabetic acidosis and coma though this lack may result from omitting insulin, infections emotional disturbances or from an increase in the severity of the diabetes by virtue of repeated insulin shocking In some 30 per cent of our children the diagnosis of diabetes mellitus is first made during an admission for acidosis or coma

The commonest precursors of acidosis and coma are anorexia nausea and vomiting and hence any one of these symptoms should alert the family and the physician In the laboratory hyperglycemia and a lowering of the serum total CO_2 content are invariably present in acidosis and coma

The mortality remains high among diabetics of all ages though it is lowest in the juveniles Deaths are particularly apt to occur in previously undiagnosed diabetics who are of course amongst the most seriously ill on admission It is in this type of patient that appropriate principles concerning routes of insulin administration the use of colloid and of sodium salts alkalinizing solutions glucose and fructose are of particular importance

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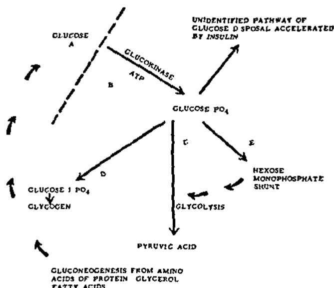


FIG 19 1 INSULIN LACK AND ITS EFFECTS ON CARBOHYDRATE METABOLISM

In insulin deficiency as in acidosis or coma glucose does not enter cells as readily (A) phosphorylation decreases (B) glycolysis is slowed (C) formation of liver glycogen diminishes (D) and the hexosemonophosphate shunt may operate at a slower rate (E) Other unidentified mechanisms of glucose disposal may also be affected (if any such be present) while gluconeogenesis is increased

sulin for adequate supplies of this sugar and hence less glucose 6 phosphate is formed In addition there is evidence that the process of ester formation may itself be impaired perhaps because adequate supplies of high energy phosphate such as adenosinetriphosphate are lacking and perhaps because the enzyme glucokinase cannot function optimally at the pH and other conditions which prevail during ketoacidosis (B in figure 19 1) (3c d) The resultant decrease in glucose ester formation naturally reduces the disposal of glucose via the usual pathways (C D and E in figure 19 1) though specific information on this point is lacking for the last of these

As these barriers to glucose utilization develop hyperglycemia increases It *becomes more pronounced despite continued lack of intake because* liver glycogen is converted to blood glucose and components of body proteins and fats are also transformed to this sugar The rise in blood sugar stems therefore from a combination of underutilization and overproduction

CHAPTER 19

Diabetic Ketosis, Acidosis and Coma: Metabolic, Endocrine, Electrolyte, and Circulatory Changes

The onset and effects of diabetic ketosis and acidosis represent a chain *of events which involves* the utilization of carbohydrate, fat and protein the secretion of hormones, the metabolism of water and electrolytes, the regulation of anion-cation balance and pH, and certain physiologic concomitants which jeopardize the life of the patient

I. Changes in the Intermediary Metabolism of Foodstuffs in Diabetic Ketoacidosis

In Chapter 1 the metabolic transformations of carbohydrate, fat and protein which result in the production of CO_2, H_2O, energy, and in the case of protein, nitrogenous end products have been described These are all altered in the patient who develops diabetic acidosis

A Alteration in Carbohydrate Metabolism in Unregulated Diabetes Mellitus

The diabetic animal or human totally deprived of insulin continues to utilize carbohydrate at the usual rates in those tissues such as the brain and nervous system which do not require this hormone (1a–d), and, at a greatly reduced rate in the others *The latter concept, first clearly* enunci [illegible] that [illegible] e [illegible] it [illegible]

tion and the increased production of glucose from protein and fat [illegible] acidosis are schematized In the absence of sufficient amounts of insulin glucose is unable to enter into cells, *i e* cross the cell wall barrier as described by Levine, Stadie and others as readily as normal (see A in figure 19-1) (3a–f, i) This may or may not be merely another facet of the process of phosphorylation of glucose which results in glucose-6 *phosphate* At any rate less glucose than usual enters those body cells which depend on in

the particular amino acids released The increased gluconeogenesis is a characteristic feature of diabetic acidosis contributing both to the hyperglycemia and to the ultimate losses of body nitrogen in urine

C Changes in Fat Metabolism in the Poorly Controlled Diabetic

1 Shift to Fat Substrate as Decrease in Glycolysis Reduces Supplies of Oxaloacetate (figure 19 3) As the relative inability to utilize glucose develops and progresses the organism shifts to fat metabolism for the energy necessary to maintain body temperature and to perform the work involved in cardiac contractions, respiration, voluntary and involuntary movement, etc These changes have been reviewed in some detail in Chapter 1 In these metabolic readjustments body stores of fat are mobilized and the glycerol portion of the glycerides is set free and converted to glucose thereby contributing another fraction to gluconeogenesis The fatty acids themselves are then broken down to acetyl CoA in the liver These can then unite with oxaloacetate and enter the Krebs cycle or be used to synthesize protein and fat Within the cycle condensation products are in turn degraded to CO_2 and H_2O with a release of energy which is stored as adenosinetriphosphate and creatine phosphate This energy is then used in the contraction of cardiac and skeletal muscle as well as in other work in the reconstitution of tissue components and in the phosphorylation of glucose (figure 19 3)

However in the diabetic patient there is a relative lack of oxaloacetate and there may be an impediment in the conversions within the citric acid cycle Krebs himself recognized the latter (7) In addition there is some evidence that the formation of adenosinetriphosphate is not as efficient as normally (3g h) Despite this the shift to a greater reliance on fat to provide energy is successful in maintaining crucial functions

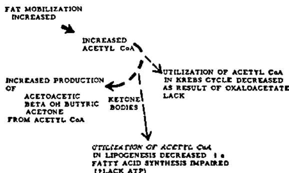


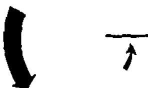
FIG 19-3 FAT METABOLISM IN DIABETIC KETO-ACIDOSIS

PROTEIN CATABOLISM



PROTEIN ANABOLISM

IN HEALTH



IN KETO ACIDOSIS

Fig 19-2 Mechanisms of Negative Nitrogen Balances in Keto Acidosis

In health catabolism and anabolism proceed at equivalent rates With acidosis and coma the breakdown of protein increases because of increased gluconeogenesis and possibly because of increased discharge of adrenocortical 11-oxysteroids Anabolism is retarded by starvation deficient glycolysis and the antianabolic effect of the 11 oxysteroids

B Protein Metabolism in Diabetic Ketosis Acidosis and Coma

1 Starvation and Loss of Proteogenic Effect of Glycolysis (figure 19 2) The uncontrolled diabetic patient is usually unable to eat and retain food This interferes with orderly replacement in the daily turnover of body protein i e anabolism is less than catabolism Studies in nondiabetic subjects indicate that the negative balance of nitrogen which develops in starvation can be minimized though not eliminated by providing the organism with extra carbohydrate (4a b) This effect is mediated through glycolysis which permits the utilization of acetyl CoA in tissue reconstruction and function When adequate supplies of carbohydrate and insulin are available and glycolysis is active a proteogenic action of insulin is readily demonstrable (5a b) This protein sparing effect is absent in keto acidosis

2 Stress as an Aspect of Acidosis and Coma In addition the diabetic *who becomes uncontrolled is in a situation of stress* one of the features of which is an excessive discharge of adrenocortical 11 oxysteroids (6a-h) (see section II) This may act to accelerate protein breakdown and definitely interferes with protein resynthesis Some of the amino acids set free by this disproportion between catabolism and anabolism are deaminated in the liver and converted to glucose The degree of conversion depends on

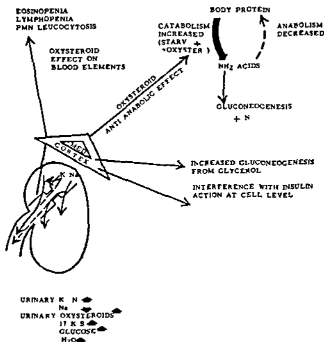


Fig 19-4 The Role of the Adrenal Cortex in Diabetic Acidosis and Coma

iese patients show an increase in the output of urinary 17-ketosteroids ther workers have made similar observations (6d)

1 **Intermediary Metabolic Effects of Increased Adrenocortical Secretion** It will be recalled from the discussion of the role of the adrenal ortex in carbohydrate metabolism in Chapter 3 that in pharmacologic osage the 11-oxysteroids interfere with or alter several facets of carbo ydrate metabolism Thus the new formation of glucose from amino acids nd perhaps from fats increases and the peripheral utilization of this sugar s partially impeded by some unidentified mechanism (6h) In animals with

ion Hence the net effect of excesses of 11 oxysteroids under these circum tances is an increase in the carbohydrate load a further impediment to lucose disposal in tissues and perhaps some amelioration of the deglyogenating process At the same time the negative balances of body pro ein already present by virtue of the starvation which occurs in acidosis

2. Excess Ketone Body Production from Excesses of Acetyl CoA Finally, in this process of shifting to fat metabolism there occurs an over mobilization of fat stores and a production of acetyl CoA in excess of the available oxaloacetate The excesses of acetyl CoA are then converted to acetoacetic and beta-hydroxybutyric acids which accumulate in body fluids, displace bicarbonate (see Chapter 17), and are excreted in the urine The acetone present in urine and in expired air is a spontaneous breakdown product of acetoacetic and beta-hydroxybutyric acid This then is the origin of the ketosis and of part of the acidosis which invariably ensue in the inadequately regulated diabetic The various interrelations are summarized in figure 19-3

3. Decreased Lipogenesis as Sequel of Diminished Glycolysis. Since the turnover of body lipid is dependent on a new formation of fats from products of glycolysis (the so-called lipogenic action of insulin (5a, b)), this process is also hindered by a deficiency of glycolysis This is supported by the finding that deprivation of insulin markedly reduces fat synthesis, *i e* the lipogenic effect is lost

II. Participation of the Endocrine System in Diabetic Ketoacidosis

At this time evidence is available that at least one of the endocrines, the adrenal, participates in the metabolic events of diabetic acidosis and coma (6a–f) The data are clear with respect to the cortex of this gland, though *if the medulla is unduly active in this complication of diabetes* (and there is no direct evidence on this point) it could contribute to the deglycogenation of the liver by activating liver phosphorylase, accelerating gluconeogenesis, decreasing muscle glycogen, and interfering, perhaps, with glucose utilization Data on other endocrine effects in acidosis or coma of diabetic origin are *either lacking or unknown* to the author

A Adrenocortical Effects in Uncontrolled Diabetes

The work of McArthur and her colleagues referred to earlier (6a, b e, f) clearly establishes that in diabetic animals withdrawal of insulin produces *marked increases in adrenocortical activity* before ketosis or acidosis is well-established These consist of a lessened sodium and an increased potassium excretion in urine, a drop in circulating blood eosinophils, and an augmented urinary output of 11-oxysteroids and 17-ketosteroids This [illegible] in figure 19-4 This can be logically viewed as a part of the [illegible]

[illegible]

figure 19-5, taken from studies by Greenman and [illegible]

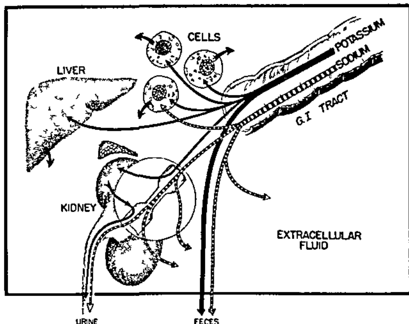


Fig 19-6 Metabolism of Sodium and Potassium in Health and the Effects of Acidosis and Coma

As shown above in health absorption of ingested or endogenous sodium from the gastrointestinal tract is virtually complete in diabetic and nondiabetic children in view of the very low content of sodium in formed feces equal to approximately 1 per cent of the intake the equivalent of 10 to 20 per cent of ingested potassium is excreted via this route with only a fraction of this attributable to losses in bacteria The anorexia nausea and vomiting which are so common in acidosis and coma interfere with intake and the last of these leads to losses of endogenous sodium and potassium in gastric secretions

In health the concentrations and total amounts of potassium and sodium in extracellular and cellular fluids remain relatively constant despite wide variations in intake However growth does result in increases in cell potassium with and in excess of the retention of cell nitrogen similarly replacement of cell protein rehydration and reglycogenation of the liver are accompanied by transfers of potassium into cells Acidosis or coma results in deficits of body sodium and potassium as a consequence of losses in vomitus and in urine Concentrations of these ions may be unchanged low or high depending on the concomitant balance of water Losses of cell nitrogen dehydration deglycogenation and interference with carbohydrate metabolism all result in negative balances of cell potassium These may be accompanied by transfers of sodium into cells

In health the adrenal cortex and other components of the homeostatic regulatory mechanisms control the renal output of sodium and of potassium in accord with the body needs and the intake of these electrolytes Acidosis and coma result in increased adrenocortical activity which increases the urinary output of potassium and of nitrogen The simultaneous trend toward sodium conservation is either partially vitiated by the osmotic diuresis attributable to glycosuria or circumvented by extrarenal losses of this ion The net effect is a deficit of extracellular sodium with impairment of circulatory efficiency and a loss of potassium with jeopardy of survival by virtue of the key role of this cation in the structure and function of cells

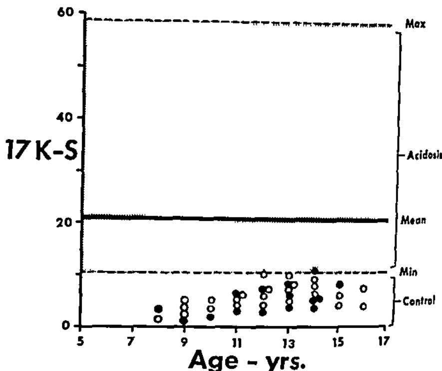


FIG 19-5 INCREASED URINARY EXCRETION OF 17 KETOSTEROIDS DURING ACIDOSIS OR COMA

The closed and open circles identify values for 17 ketosteroid excretion in healthy nondiabetic boys and girls respectively Shaded area encompasses the maximum and minimum values found in a group of 12 diabetics in acidosis or coma 5–17 years of age (6c) Though not shown in above figure the 17 ketosteroids decreased to the range of control values following recovery

and coma are aggravated by the 11 oxysteroids as is the mobilization of fats

III Electrolyte and Water Transfers During the Development of Diabetic Acidosis

Diabetic ketosis or acidosis is frequently associated with or preceded by anorexia nausea and vomiting This interferes with the intake of food and fluids and results in starvation (8a–p) and dehydration (9a–e) which by themselves produce deficits of body water and electrolytes In addition such patients lose electrolytes and water via vomitus sweat urine and perhaps into the gastrointestinal tract if dilatation occurs Transfers of the chief cations (sodium and potassium) are summarized in figure 19 6

TABLE 19 1

Electrolyte content of gastric secretions

Authors	Subjects (Number)	Secretion	No analyses	Electrolyte Concentration (mEq /L)			
				Na^+ Mean (min max)	K^+ Mean (min max)	Ca^{++} Mean (min max)	Cl Mean (min max)
Bernstein (10a)	Healthy young adults	Over night gastric	50	49 (19 70)	11 6 (6–17)	3 6 (2–5)	
		A M gastric	41–82	42 (16–59)	9 7 (6 13)	3 3 (2–5)	
Lesser and Pareira (10b)	Pre op patients	Gastric	9	66 5	13 7		100 6
Lans et al (10c)	Peptic ulcer (24)	Gastric	72	56 (21–82)	12 6 (6–26)		126 (76–157)
	Gastric cancer (13)	Gastric	48	61 (24–91)	10 2 (7 25)		58 (39–110)
	p Vagot (4)	Gastric	13	72 (32 126)	12 1 (5–25)		56 (36–92)
	Resections (21)	Gastric	40	136 (82 167)	5 3 (2 9)		98 (38 142)
	Nongastric pts (41)	Gastric	64	113 (46–117)	4 6 (3 16)		104 (24 127)
McGowan and Stanley (10d)	Peptic ulcer	Gastric	12	(20–90)	(5–19)	(0–2)	(80–152)
Lockwood and Randall (10e)	Surg patients	Gastric		60 4 (9–116)	9 2 (0–32)		84 0 (8–154)

centrations of sodium and chloride in gastric juice may be as high as those in extracellular fluid whereas potassium levels may exceed those in plasma or serum concentration by several fold (10a–e) Though observations in diabetic acidosis are scanty, they are in keeping with these values (12) Furthermore it should be noted that the increased gastric secretion following attempts to ingest food and fluids may actually increase the volumes of gastric secretions which are lost by subsequent vomiting

2 *Urine volumes are greatly increased as a consequence of the hyperglycemia* with presentation of glucose loads which exceed the normal reabsorptive capacity of the tubules This results in an osmotic diuresis induced by the unreabsorbed glucose within the lumen of the individual tubules which sweeps out electrolytes that might otherwise be reabsorbed This relationship is clearly shown in correlations of urine flow with electrolytes and nitrogen output in a group of diabetic children in acidosis or coma (13) (figure 19 7) Large amounts of body chloride sodium potassium nitrogen, magnesium, phosphate and undoubtedly many other constitu

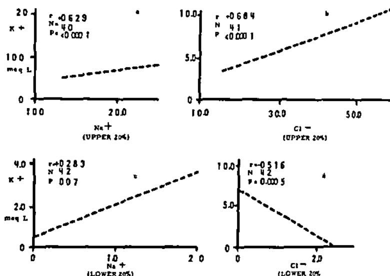


FIG 19 7 INTERRELATIONS OF URINARY POTASSIUM CHLORIDE AND SODIUM IN DIABETIC ACIDOSIS AND COMA IN CHILDREN

There is a definite positive correlation between the urinary output of sodium and potassium and of chloride and potassium when urinary sodium and chloride are high (a and b of above figures) At low levels of sodium and of chloride the correlation is much less or absent (figures c and d) (13)

A Electrolyte Losses During the Development of Acidosis

1. Gastric Secretions contain chloride sodium potassium and water in addition to hydrogen ions (10a–e) The losses of the first four of these create deficits which must be replaced from exogenous sources The hydrogen ion loss creates no problem and may at first sight be looked upon as a benefit since in uncompensated diabetic acidosis hydrogen ions are present in excess Actually such losses of hydrogen ions are promptly replaced from H_2CO_3 and other sources if the disturbances of anion cation balance described earlier persist Vomiting is a very common occurrence at the onset of acidosis irrespective of whether it represents intrinsic gastrointestinal disease (see Chapter 24), an intercurrent gastroenteritis or a manifestation of the ketosis acidosis It occurred in more than three quar

The potential magnitude of the electrolyte losses as a result of vomiting can be estimated from the composition of the gastric fluids of fasting healthy volunteers and patients From table 19 I it can be seen that con

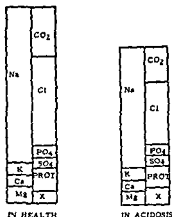


FIG. 19-8 GAMBLE DIAGRAMS OF ELECTROLYTE CHANGES IN DIABETIC ACIDOSIS OR COMA
The anion-cation disturbance in ketoacidosis

a) Accumulation of acetoacetic and beta hydroxybutyric acid displaces bicarbonate
b) Rise in undetermined acids as result of renal failure decreases bicarbonate
c) Depletion of sodium by external losses and decreases in the osmotic activity of cell base are present

In keto-acidosis displacement of bicarbonate by a b c decreases the common ion effect (buffer effect) and permits greater ionization of H_2CO_3 to yield more H^+ ions and lower pH The organism responds by increased respiratory output of CO_2 which decreased formation of H_2CO_3

VI. The Known and Unknown Physiologic Effects of the Water and Electrolyte Deficits and the Anion Cation Disturbances of Diabetic Acidosis

A Metabolic Acidosis

Metabolic acidosis which becomes uncompensated when the buffering and adjustment mechanisms are no longer capable of maintaining hydrogen concentrations within normal limits may produce death However, we have seen a patient with pH reduced to 6 9 and many others with pH values of 7 1, 7 2 who have recovered following adequate therapy (21)

B Water Deficits

Pure dehydration produces occasional disturbances in circulatory efficiency as evidenced by changes in the blood pressure cardiac output, circulation time, and peripheral resistance (figure 19 9) (22a, b) These reflect the effects of a decrease in the water of the plasma and of the extracellular fluid and cells, since deficits incurred initially via the extra-

flects the degrees of the pretherapy deficits Results of such studies are given in table 19-II and may be summarized as follows (18) in terms of each kilogram of body weight, a reference device which is essential in view of the differing ages and sizes of children, deficits range as follows total water 87 to 114 ml and extracellular water 42 to 110 ml per kg, chloride 2 5 to 9 5 mEq per kg, sodium 5 1 to 13 3 mEq per kg, potassium 4 9 to 6 1 mEq per kg, and nitrogen 0 09 to 0 9 gm per kg of body weight

It has long been recognized that organic acid soluble phosphorus compounds are broken down and extensive deficits of body phosphate develop in acidosis and coma (19a–c) The drop in serum inorganic phosphorus may not be evident prior to therapy (20a) because of the concomitant greater deficit of water and because of release of phosphate from cells to the extracellular fluids prior to excretion in the urine Hypophosphatemia then appears quite regularly during therapy with phosphate free solutions The data of Franks *et al* indicate approximately 90 per cent retention of administered phosphate during the first 24 hours (20b)

V. Changes in the Anion-Cation Balance of Serum or Plasma in Cellular Fluids in Diabetic Coma

As pointed out in Chapter 17 the accumulation of anions, the external losses and internal transfers of electrolytes, and the bicarbonate and other buffer changes which occur in acidosis and coma produce profound changes in the anion-cation pattern of the serum

The accumulation of excesses of ketone bodies in body fluids as a consequence of overmobilization of fats has also been mentioned These exist in body fluids as anions, *i e* negatively charged ions As the ketone bodies the inorganic phosphates and other anions increase in concentration, bicarbonate decreases and a metabolic acidosis results with an increase in hydrogen ions via the common ion effect described in Chapter 17 This becomes intensified as sodium is lost via vomitus urine or other routes and transferred into cells as a consequence of the acidosis or in connection with losses of cell potassium (9b, 20a) The resultant decreased levels of sodium bring about a further decline in bicarbonate Hence the metabolic acidosis of diabetes is a result of increases in anions (ketone bodies and phosphate) and a loss of the chief cation (sodium) (see figure 19 8)

When the body buffer systems and the ventilatory and renal regulators are no longer able to compensate fully for the metabolic acidosis, Kussmaul breathing appears The deep breathing produces a secondary respiratory alkalosis which increases the loss of CO_2 from the body, decreases P_{CO_2}, diminishes H_2CO_3 formation and thereby decreases the hydrogen ion concentrations

C Sodium and Chloride Deficits

Abrupt removal of extracellular sodium and chloride in sufficient amounts by one of a variety of techniques produces prompt circulatory collapse akin to the shock seen after massive trauma, burns, or hemorrhage (22a, 23b-h) This is illustrated in figure 19-10 taken from studies by the author and his colleagues Hence deficits of sodium and chloride of the type which occur in diabetic acidosis and coma predispose to or precipitate a decrease in cardiac output, in blood pressure, and in circulation rate This is supported by our finding of a high incidence of hypotension in correlation with hyponatremia in the 188 cases of diabetic coma cited earlier (11)

It should be kept in mind that it is the absolute deficit as well as the concentration deficit of sodium and chloride that is important in the genesis of this circulatory collapse since raising the concentrations back to normal, without restoring the total amount of these electrolytes, has no beneficial effect upon the circulatory collapse (24) (figure 19 11)

D Potassium Deficits

It is well to point out that deficits of the total amount of body potassium can and do coexist with elevated or normal concentrations of this ion in

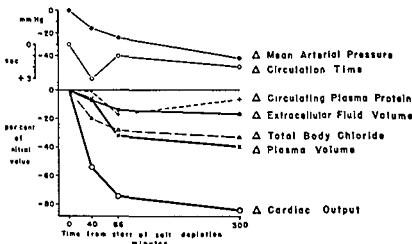


Fig 19-10 Sequence of Body Fluid and Circulatory Changes in Acute Experimental Depletion of Extracellular Electrolytes

The removal of extracellular electrolytes and of sodium and chloride in particular produces prompt circulatory collapse which is still present at the end of 5 hours of observation (22a)

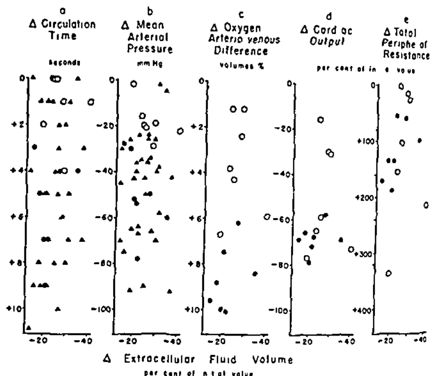


FIG 19 9 COMPARISON OF CIRCULATORY EFFECTS OF PURE EXTRACELLULAR SALT DEPLETION AND OF PURE WATER DEPLETION

Closed circles and closed triangles identify animals depleted of extracellular electrolytes by the Darrow-Yannet technique, open circles represent water depletion produced by urea diuresis Losses of extracellular electrolytes regularly prolong the circulation time lower the blood pressure, and decrease the cardiac output In water depletion circulatory efficiency is well maintained (22a)

cellular fluid are ultimately distributed through all of the fluid compartments This is a consequence of the permeability of all body fluid spaces to water and the prompt movement of water from one compartment to another in response to changes in osmotic pressure differences This subject has been discussed in detail elsewhere by Elkinton and Danowski (22b) With progressive dehydration, deficits of water within the cells of the nervous system become critical and respirations cease at a time when the circulation is still well-maintained (23a)

However in the diabetic in coma the above terminal event does not usually supervene because critical deficits of electrolytes develop in addition to the water deficits and precipitate circulatory collapse

1. Electrocardiographic and Other Effects of Potassium Disturbances Encountered in Diabetic Coma. When the potassium levels are low in extracellular fluid, electrocardiographic changes consisting of flattening of the T wave and the so called prolongation of the Q-T interval frequently appear (26a–c) In addition such patients may at times develop marked weakness or flaccid paralysis of the voluntary musculature (26b, 27) The frequency of these two phenomena is conditioned, however, by changes in other electrolytes (thus low calcium levels cancel the effects of low potassium levels on the electrocardiogram) (28a–d) and by other factors We have seen only one unequivocal instance of flaccid paralysis in acidosis or coma in children It should be pointed out that specific weakness present on this basis might well be masked by the general prostration, debility and inability of the coma patient to cooperate

Patients with deficits of potassium who have elevated extracellular concentrations of this ion will show in varying degree the ECG evidence of potassium cardiotoxicity first described by Winkler, Hoff and Smith (29a) These are usually limited to peaking of the T-wave though rises will induce the well-known though variable sequence of loss of P waves, prolongation and disruption of the QRS complex and cardiac standstill at levels approximately threefold above normal (29b), i e around 12 mEq per liter Such patients may presumably also show flaccid paralyses of the type described with hyperkalemia in renal failure (26b), though no such specific instance has been reported

The deficits of cell potassium which occur in diabetic acidosis may produce cellular necrosis of the type described in the heart and in skeletal muscles on potassium-free regimens (30a, b) Since cellular integrity is thereby destroyed function and survival are jeopardized Evidence is available that death may ensue in patients as a consequence of potassium deficits, even though the patient is otherwise recovering successfully from coma (30c)

E Phosphate and Magnesium Deficits

Though there is good evidence that these ions are lost in large amounts during diabetic coma, there is as yet no definite evidence that these represent specific hazards of the type seen with water, sodium, or potassium depletion

F The Unidentified Deficiencies

It is always well to remember that availability of the necessary analytic techniques plus knowledge of the effects of certain deficits tends to overemphasize their relative importance in diabetic coma However, the co

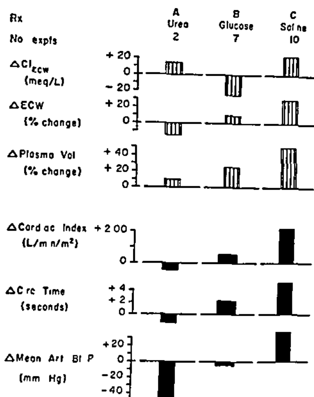


Fig 19 11 Therapy of Sodium Chloride Depletion

Restoration of concentrations by urea induced diuresis only resulted in further circulatory deterioration Glucose solutions restored extracellular water and plasma volumes (Δ ECW and Δ Plasma Vol) with some improvement in cardiac index circulation time and blood pressure Improvement was most marked however following saline replacement which restored both the concentration and the volume of the extracellular fluids (24)

serum This is clearly evident from the repletion studies in children from this laboratory referred to earlier (17a 20a) All of the children retained potassium yet serum potassium levels were elevated in only a minority within normal in most and below normal in only a few of the patients (see figure 18 8) This is merely a reflection of the fact that the actual [illegible] than the concomitant deficits

of renal failure in the adult group

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existence of other changes, at present unrecognized, may be equally crucial in terms of survival

Summary

The decrease in carbohydrate utilization in diabetic acidosis is accompanied by *increased* gluconeogenesis and decreased proteogenesis and lipogenesis There is evidence of increased adrenocortical activity (urinary 17-*ketosteroid output* and serum corticoid levels rise) which increases gluconeogenesis *from* amino acids and further accentuates the negative balances of nitrogen and the mobilization of fat attendant upon the acidosis and the starvation Presumably the adrenocortical oxysteroids further interfere with the peripheral action of insulin though they may still facilitate liver glycogenation under the conditions of ketosis and acidosis

Deficits of body water are incurred during the development of acidosis and coma as a consequence of inadequate intake resulting from anorexia nausea, and vomiting, and an increased output of water during emesis overbreathing, and polyuria Sodium and chloride depletion develops through losses of these ions in gastric secretions and urine Interruption of carbohydrate metabolism, liver glycogen depletion, cellular dehydration and starvation all lead to negative balances of body potassium though the level of extracellular potassium is determined by the external and internal transfers of potassium in relationship to the deficit of body water In contrast to the disturbances in water, sodium chloride and potassium metabolism, losses of phosphate, magnesium and other constituents have not thus far been shown to have physiologic concomitants

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CHAPTER 20

Therapy of Diabetic Acidosis and Coma

From the discussion in the preceding chapter it will be recalled that in acidosis and in coma there occurs a decrease in carbohydrate utilization with a shift to fat metabolism, loss of body protein, accumulation of ketone bodies, hyperglycemia, glycosuria, and ketonuria with increased urinary output of water and electrolytes, dehydration with extracellular and cellular electrolyte deficits as a consequence of renal and extrarenal losses, disturbance of the anion-cation pattern with possibly a drop in the pH of body fluids and finally, circulatory deterioration Therapy consists of the administration of insulin and, later, of glucose, replacement of water and electrolyte deficits, infusion of colloid solutions to restore circulatory efficiency, and, finally, resumption of oral intake and a full diabetic diet In the course of these procedures any intercurrent or associated disease process should be treated and hypoglycemia, excessive amounts of water and electrolytes, iatrogenic alkalosis, and recurrence of vomiting are to be avoided

I. The Use of Insulin in Diabetic Acidosis and Coma

The *sine qua non* of the therapy of acidosis and coma is the administration of rapid acting insulin in adequate amounts *If the diagnosis is certain the first dose should be administered by the physician or family prior to transferring the patient to the hospital* This and other pertinent aspects of therapy are summarized in table 20-I

A In the Early Hours of Therapy

Upon admission, if treatment has not been started earlier, 100 or 50 units of insulin are injected in part subcutaneously and in part intravenously while blood is withdrawn for analyses and infusions of saline or other sodium salts and of colloid solutions are begun The intravenous route obviates delay resulting from slow absorption, the losses of part of the intravenous insulin in urine are replaced in subsequent therapy and are therefore of no consequence (Ia–c) At the end of the first hour further *amounts of insulin are given If the patient is in severe coma, and the* hyperglycemia is between 400 or 800 mg per cent, 100 or 50 units are again injected In the milder cases and especially in young children 35 units are

TABLE 20 I

Outline of Therapy of Diabetic Acidosis or Coma

A Nothing *per os*, collect all urine, measure intake and output, obtain sample of venous blood in oxalate for measurement of whole blood NPN and blood sugar and under oil for determination of total CO_2 content, pH, and levels of chlo [illegible]

[illegible]

ured

B Immediate administration of rapid acting insulin (even before admission to the hospital) by vein and subcutaneously 100 or 50 units at zero time and repeated at 1, 2, 3 hours at the same or at a reduced dosage depending on the results of blood and serum analyses, *i e*, greater amounts of insulin to be given the higher the blood sugar, the greater the decrease in serum total CO_2 content and pH

C Immediate administration of 0 9 per cent sodium chloride or similar solutions by vein keeping in mind body weight differences (table 20-IV) and the recommended ceiling values for rates of administration (table 20 III) Alkalinizing solutions ($NaHCO_3$ or Na lactate) are reserved for seriously ill patients with *significant decreases in pH, since they deprive the clinician of the* serum total CO_2 content as an index of improvement and expose the patient to inadvertent alkalosis

D Routine infusion of dextran in saline, of plasma, or other colloid solutions to help combat the salt depletion shock which may be present even though evidences of obvious circulatory collapse are lacking

E Repeat blood sampling at 3 or 4 hours and serial analyses of all urine for sugar and ketone bodies as guide to further insulin therapy if blood sugar is decreasing and serum CO_2 content and pH are rising insulin dosage is decreased to 25 units or less at intervals of two hours

F [illegible] 500 cc of 5 per

[illegible]

tions (peaking of T wave, loss of P wave, and disruption of QRS complex indicate potassium intoxication) should be kept in mind

G Glucose or fructose infusions, 5 to 10 per cent in water, with or without buffered potassium phosphate should be started once blood sugar begins to fall or earlier in patients with only slight hyperglycemia to avoid *hypoglycemia* during recovery

H Resumption of oral intake after six to 12 hours of therapy when overbreathing has ceased, consciousness has returned, and patient can retain fluids *tea with* sugar, ginger ale, milk, etc Continue infusions at a slow rate until possibility of vomiting has passed

I Repeat blood and serum analyses at 12 and 24 hours and p r n as guide *in individualization* of therapy, *i e* extra glucose in hypoglycemia, additional potassium in persistent hypokalemia, etc

adequate During the third and fourth hours 25 to 35 units are given each time

B Recovery and Other Indices in Determining Subsequent Insulin Dosage

At the end of the fourth hour blood sugar serum CO_2, other electrolyte, and ketone levels are obtained as a guide to further insulin administration. If the patient is responding successfully to therapy, i e the blood sugar has begun to decline and a rise is evident in the CO_2 content, the dosage of the hormone is reduced to 15 or 20 units and the interval between injections lengthened to two hours The therapist is supported in these decisions by clinical evidences of recovery such as restoration of consciousness and decrease in overbreathing Otherwise the larger amounts used earlier are repeated until the various favorable signs appear At this point it is usually necessary and wise for reasons presented in section III to start the parenteral administration of glucose or fructose solutions in volumes sufficient to provide 20 to 30 gm of carbohydrate each hour These should be continued beyond the point of initial resumption of oral carbohydrate intake, since some of the patients may subsequently vomit

At the end of 18 to 22 hours of parenteral therapy the insulin dosage averaged 78 to 159 units in our 0–4 4–8 8–12 12 16 year old groups admitted with initial serum total CO_2 content reduced to 10 mEq per liter or less (see table 20 II) (2a c) This is less than the 225 units administered to a group of adults over the same period of time (3) It must be emphasized however that members of either group may need amounts much less or much greater than the recorded average Finally some patients who develop insulin resistance may require huge amounts of insulin, [illegible] to 56 000 units (4a–c) Fructose therapy incidentally does not reduce [illegible] requirement in such cases (4f g)

1 **Insulin Resistance** Electrophoretic studies in a few such pati[illegible] with insulin resistance have revealed high levels of gamma globul[illegible] associated with a reduction in the hypoglycemic action of insulin (4[illegible] Therapy with ACTH decreased the hypergammaglobulinemia [illegible] resistance to insulin It is not possible to state at this time tha[illegible] the sole mechanism of insulin resistance and that explanations [illegible] in the past such as antibody formation excessive insulinase [illegible] endocrinopathy diminished phosphate reserves, etc are to be [illegible] (4k–u)

C Danger of Hypoglycemia as Recovery Progresses

Particular care must be taken to avoid insulin hypoglycem[illegible] with short acting insulin shocks may occur many hours [illegible] the larger doses of the hormone The hypoglycemia is mo[illegible]

TABLE 20 II

Summary of Therapy in Diabetic Acidosis and Coma in Juvenile Diabetics Admitted with Serum Total CO_2 Content of 0–10, and 10 1–15 mEq per Liter (2c)

	Age Group	Average Age	No of Cases	Hours of Rx	Average Therapy
	years	*years*			
Insulin					*units*
0–10 mEq /L	0–4	2 2	22	22 5	78 5
group	4–8	6 4	14	20 4	78 8
	8–12	9 9	31	20 2	146 4
	12–16	13 8	49	18 6	158 6
10 1–15	0–4	2 6	6	8 2	41 7
mEq /L	4–8	6 0	8	26 4	71 5
group	8–12	9 8	12	15 1	68 8
	12–16	13 0	5	13 7	43 4
NaCl					*gm*
0–10 mEq /L	0–4	2 1	20	22 2	9 7 (167 mEq Na, 167 mEq Cl)
group	4–8	6 2	13	21 2	14 1 (243 mEq Na, 243 mEq Cl)
	8–12	10 1	34	19 4	13 2 (228 mEq Na, 228 mEq Cl)
	12–16	13 9	44	16 3	17 2 (297 mEq Na, 297 mEq Cl)
10 1–15	0–4	2 6	5	8 1	6 8 (117 mEq Na, 117 mEq Cl)
mEq /L	4–8	6 3	10	17 0	9 4 (162 mEq Na, 162 mEq Cl)
group	8–12	10 1	12	15 8	14 2 (245 mEq Na, 245 mEq Cl)
	12–16	13 0	5	13 6	9 4 (162 mEq Na, 162 mEq Cl)
Water					*liters*
0–10 mEq /L	0–4	2 1	21	21 6	2 1
group	4–8	6 2	14	20 9	2 8
	8–12	10 0	35	19 0	2 9
	12–16	13 9	44	16 3	3 2
10 1–15	0–4	2 6	5	8 1	1 4
mEq /L	4–8	6 3	10	17 0	2 5
group	8–12	10 1	12	15 8	2 7
	12–16	13 0	5	13 6	2 2
Glucose					*gm*
0–10 mEq /L	0–4	2 1	21	21 6	99 7
group	4–8	6 2	14	20 9	162 9
	8–12	10 0	35	19 0	154 4
	12–16	13 9	43	16 3	147 9
10 1–15	0–4	3 0	4	9 1	56 2
mEq /L	4–8	6 7	8	19 1	104 4
group	8–12	10 1	10	18 1	156 8
	12–16	13 0	5	13 6	88 2
Potassium					*mEq*
0–10 mEq /L	0–4	2 3	9	21 8	53
group	4–8	7 4	5	30 1	64
	8–12	10 1	18	22 2	73
	12–16	14 2	18	19 9	59
10 1–15	0–4	2 5	1	10 5	60
mEq /L	4–8	8 0	1	10 0	15
group	8–12	9 7	4	24 2	82
	12–16	11 9	1	5 5	40

TABLE 20 II (Continued)

	Age Group	Average Age	No of Cases	Hours of Rx	Average Therapy
	years	*years*			*mEq*
Phosphate					
0-10 mEq /l	0-4	2 3	7	18 6	51 1
group	4-8	7 4	4	28 6	60 0
	8 12	10 0	16	22 3	71 9
	12 16	14 1	17	19 3	60 6
10 1 15	0-4	2 4	1	10 5	60 0
mEq /l	4-8	8 0	1	10 0	15 0
group	8 12	9 7	4	21 2	82 5

between the twelfth and twenty fourth hour of therapy (2c 3) Another measurement of blood sugar CO_2 content ketone potassium and other electrolyte levels should be made at the twelfth hour as a further guide to therapy The hypoglycemia is not to be prevented by restriction of insulin in the early periods but rather by adequate coverage with carbohydrate in the later hours Again sole reliance upon an oral intake may prove dangerous since vomiting and delays in assimilation do occur *Particular care must be taken to assure communication by the nurse of knowledge of any interference with intake to the physician in charge day or night*

As insulin therapy proves successful the urinary ketone bodies decline progressively though glycosuria remains profuse Though in some patients acetone and diacetic acid may disappear by the tenth hour in others ketosis will be evident for as long as two days (table 20-V) Once the patient is convalescent from acidosis and coma and this usually occurs the day after admission the pre-coma amounts and forms of insulin are resumed but these may have to be supplemented several times a day in accordance with the results of blood sugar and ketone and urinary ketone and sugar levels

II The Administration of Solutions of Sodium Salts

The provision of an adequate intake of sodium and water will largely remedy the circulatory collapse resulting from sodium depletion and dehydration (3 5a–c) and provide water for adequate renal correction of the acidosis which occurs secondary to the accumulation of unmeasured anions and the loss of sodium For this purpose 0 9 per cent sodium chloride in water (table 20 I) 0 45 per cent sodium chloride in five per cent glucose one sixth molar sodium lactate sodium bicarbonate or Ringer s lactate have usually been employed There are advantages and disadvantages to all of these and to remedy the latter a number of other preparations, such

as Darrow's (6a, b), Butler's (6c–f) and Talbot's (6g, h) solutı
those suggested by Elkınton and Taraıl (6ı, j) are available

A The Virtues and Limitations of "Physiologic" and of Diluted S

Sodium chloride, 0 9 per cent, is readily available and can be use beginning of replenishment since deficits of these two ions devel currently in acidosis and coma However, the one-to one ratio of t ions is unphysiologic, since within the body the sodium and chlor present in the proportion of approximately three to two This pres additional load of chloride for urinary excretion and, if renal and ex capacity proves inadequate, the excess anion will result in an chloremic acidosis superimposed upon the pre existing metabolic a (7) Furthermore the high level of the two ions in 0 9 per cent 154 mEq per liter, does not provide adequate volumes of water pletion and for urinary excretion Hence, it is well to limit the use per cent saline to the initial phase of therapy, administering one liters to the teenage or young adult diabetic Then an *in vitro* or mixture of hypotonic saline is used, *i e* 0 45 per cent saline in 5 p glucose, or 5 per cent glucose in water is administered concurrentl *0 9 per cent saline, or one of the pediatric hypotonic solutions can b* The one-half strength saline in 5 per cent glucose, the other hyp fluids, or 5 per cent glucose should not be used, however, as the fluid since it will further dilute the depleted sodium stores intro thereby the hazard of water intoxication and convulsions and cont a carbohydrate load before utilization of glucose is restored The dosage of sodium and of chloride ions in the first 24 hours of ther the Pittsburgh series is shown in table 20-II

B The Use of Sodium Lactate and of Ringer's Lactate

The use of one-sixth molar lactate or equivalent amounts of bicarb produces prompt correction of the acidosis and enhances the act insulin (8a–c) but fails to provide chloride and water These sol *also deprive the physician of one of the useful indices of recovery,* rise in serum total CO_2 content which occurs as sodium levels are re and ketone bodies are cleared from the body fluids (figure 20 1) over, a real hazard is present in that a therapy-induced alkalosis suddenly replace the metabolic acidosis (8d–g) It is true this c avoided by serial measurements of pH along with serum total CO_2 tent, but it further complicates therapy Hence the use of bicarb or one sixth molar lactate should be reserved for the severely ill pa in whom marked lowering of pH is present and in those with renal

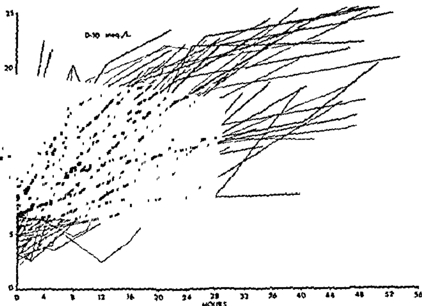


FIG 20-1 CHANGES IN SERUM TOTAL CO_2 CONTENT DURING THERAPY OF ACIDOSIS OR COMA IN PITTSBURGH SERIES OF JUVENILE DIABETICS ADMITTED WITH SERUM TOTAL CO_2 OF 10 MEQ PER LITER OR LESS (2c)

tion inadequate for clearance of ketone bodies In some clinics, however, these salts are employed routinely by vein or by gavage following aspiration of stomach contents (9a–g) We have never used the latter procedure an[illegible] former *for severely ill coma patients* with marked lowering of

[illegible] less chloride. This meets the [illegible] ; but unless used in conjunction with 5 per cent glucose [illegible] permit adequate rehydration It also interferes with the use of the serum CO_2 as an index of recovery. The small amounts of potassium and calcium ions in this solution (*four milliequivalents per liter of each*) cannot replenish deficits.

C Reliance on Hypotonic Solutions of Sodium in Mild Acidosis

The dilute solutions proposed by Butler and Talbot (6c–h) represent a compromise between prompt replacement of sodium and chloride deficits and the obvious need for water The other electrolytes (potassium, calcium, magnesium, and phosphate) are present in amounts sufficient to cancel

TABLE 20 III

Homeostatic limits in parenteral fluid therapy

	Floor	Ceiling
Glucose (gm /sq m /24 hr)	75	350
Sodium (mEq /sq m /24 hr)	10	225
Potassium (mEq /sq m /24 hr)	10	225
Phosphorus (gm /sq m /24 hr)	0 3	2 0
Water (cc /m osm solute)	0 7	10 0

TABLE 20 IV

Approximate relationships of body weight

Body Weight		Surface Area
kg	*lb*	*Sq m*
2	4 4	15
5	11 0	25
10	22 0	45
15	33 0	6
20	44 0	8
30	66 0	1 05
40	88 0	1 3

moderate deficits They can be employed to advantage in mild acidosis The "floor" and "ceiling" values for rates of water and electrolyte administration advocated by these workers (table 20-III), and the surface area conversion (table 20 IV), provide a useful guide to volumes to be employed, but it must be remembered that pre existing deficits and continued urinary losses raise the minimal value while circulatory and renal diseases lower the ceiling

D Use of More Concentrated Solutions of Sodium and Potassium in Later Phases of Treatment

The solutions suggested by Elkinton and Tarail (61, j) provide for the simultaneous replenishment of potassium and hence should be used in the initial phase of therapy only under special circumstances when potassium intoxication is not a danger

The 24 hour input of all fluids in our pediatric acidosis and coma series of cases falls within the ceiling limit (table 20-II)

In essence therefore we feel that it is best to rely on 0 9 per cent saline at the start of therapy and then shift to hypotonic saline or one of the other mixtures once the deficits are partially replaced Serial sodium and chloride

values in acidosis and coma under such therapy are shown in figures 20 2 and 20 3 Under this scheme the needs for other constituents such as water, glucose, potassium, and phosphate are met individually at the optimal points during therapy

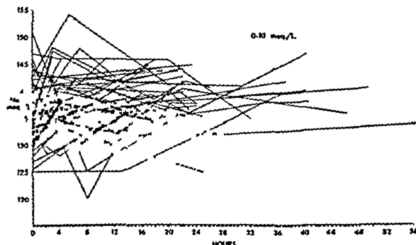


Fig. 20 2 Changes in Serum Sodium During Therapy of Juvenile Acidosis or Coma in Patients Admitted With Serum CO_2 Content of 10 mEq per Liter or Less

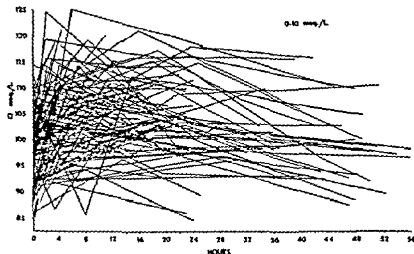


Fig. 20-3 Changes in Serum Chloride During Therapy of Juvenile Acidosis or Coma in Patients Admitted With Serum CO_2 Content of 10 mEq per Liter or Less

III. The Need for Glucose and Other Monosaccharides in Aqueous (Non-Saline) Solutions

As indicated in Chapter 18, it is now generally agreed that safe and adequate therapy of diabetic acidosis includes the use of glucose or fructose (table 20-II) At one time it was argued that such patients already have a plethora of sugar and that additional amounts result in increased water and electrolyte losses, circulatory collapse, and even death (9b, 8f, 10a–h) The first of these arguments is of little moment since the patient is already receiving replacement amounts of water and of the chief ions, and hence a little more will readily cover the additional urinary losses if they do occur The second reason formerly advanced against glucose administration was based on the observation that patients receiving glucose and water died (10a) At that time it was not appreciated that this was not attributable to the use of this particular solution but rather that the patient was simultaneously deprived of replacement electrolytes and the subcutaneous administration of glucose in water only further aggravated the electrolyte depletion by sequestering sodium and chloride (10i) Circulatory collapse was thereby precipitated or aggravated This latter effect is clearly demonstrated in figures 19 9 and 19 10 in Chapter 19, based on studies in animals and in humans These facts are now generally recognized (8g, 10j–r) and the workers who initially opposed the use of glucose now employ it routinely once the blood sugar has begun to decrease There are several cogent arguments for the administration of glucose

A Arguments for the Use of Glucose or Fructose

1. Deficiency of Carbohydrate Stores in Coma First, the patient's carbohydrate stores are greatly depleted despite the hyperglycemia The glycogen in liver, muscles, and presumably other tissues is greatly diminished in acidosis (11a) The sugar in blood and in the extracellular fluid (glucose is largely excluded from cells in acidosis (10q) because the usual processes of disposal, *i e* glycolysis, glycogenation, and catabolism via the hexose monophosphate shunt are not operative) are limited in amounts *Thus even with blood sugars of 700 mg the total amount of sugar in a*

t

whereas it is actually less because of dehydration This amount prove woefully inadequate as substrate once the usual or accelerated rates of insulin action and carbohydrate metabolism are re established

2 Hyperglycemia as a Facilitator of Glucose Disposal Second there is ample evidence that hyperglycemia alone or in the presence of insulin aids the disposal of carbohydrate via the metabolic pathways

cited earlier (11b) It accelerates glycolysis, facilitates reglycogenation of the liver, and increases the rate of use via the monophosphate shunt. This beneficial effect can be looked upon as another manifestation of the law of mass action, i e within certain parameters increasing the concentration of one of the participants in a reaction increases the rate of the reaction Replenishment of liver glycogen in turn cancels excessive ketone body production (11c)

3. The Prevention of Insulin Shock. Third, the danger of hypoglycemia is very real during the recovery phase of acidosis In our previous series of 188 patients (3) hypoglycemia or clinical shocking occurred in 20 per cent of the fatal cases between the twelfth and twenty-fourth hour even though the treatment regimen called for glucose In these instances however, the prescription was not carried out because of vomiting, infusion difficulty or misunderstanding In the last regard particular care must be taken to alert the nursing personnel to notify the physician in charge when carbohydrate is not being received even though this means interruption of sleep after a busy night or day The hypoglycemia results of course from the acceleration of carbohydrate disposal by the insulin given in the earlier hours of therapy even though the dosage is later drastically reduced

For these various reasons glucose should be started as soon as the blood sugar begins to fall, i e about the third or fourth hour In some patients in whom admission blood sugars are low i e below 300 mg per cent, it can be started as soon as this fact is known Obviously there will be patients in whom the response to therapy is not adequate and glucose is not begun until later The total glucose input in our series of acidosis and coma patients is shown in table 20 II

B The Value of Fructose and Fructose and Glucose

Several arguments have been advanced for the use of fructose or invert sugar (equal parts of glucose and fructose) in place of glucose (12a–h) The fructose can enter the glycolytic cycle without the intervention of insulin it forms glycogen more readily and the renal tubules can reabsorb fructose independent of their maximal capacity to reabsorb glucose This last factor minimizes glycosuria The net gain in carbohydrate metabolism with the use of fructose is limited however by the fact that only 20 per cent or less of this sugar escapes conversion to glucose via the Embden-Meyerhof Parnas pathway (see Chapter 1)

C Types of Glucose and Fructose Solutions

The glucose or fructose can be given as a 5 per cent solution in normal saline by vein or by hypodermoclysis, as 5 per cent glucose or fructose in 0 45 per cent saline by vein, or as a 5 or 10 per cent solution in water by vein

The latter two solutions must not be given subcutaneously when salt depletion shock is still a danger, even if combined with hyaluronidase It should be remembered that if the 0 9 per cent saline solutions of these sugars are used there is no provision for replacement of body water

IV. Therapy with Potassium and with Phosphate

It has been indicated in the previous chapter that deficits of body potassium are incurred in diabetic ketosis by virtue of external losses in urine and vomitus during periods of inadequate or absent intake (2a b 13a h) Though the immediate source of this negative balance is the extracellular fluid the ultimate origin is largely cellular Known factors leading to losses of this electrolyte from cells include starvation with protein breakdown dehydration deglycogenation and interruption of carbohydrate metabolism (see figure 19 6) (2a b 14a–c) There are undoubtedly other as yet unidentified causes The net effect is a loss of this key component of cells in amounts which ultimately become crucial and jeopardize function and structure with evidence of cell necrosis It has already been pointed out that hyperkalemia may mask the existence of such deficits either because the loss of water is greater or because the movements of potassium from cells into the extracellular fluid exceed the rate at which it is being lost to the external environment The latter is particularly apt to be true

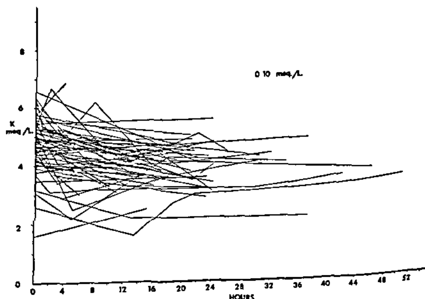


Fig 20-4 Development of Hypokalemia During Recovery From Acidosis or Coma of Patients Admitted with Serum Total CO_2 Content of 10 mEq per Liter or Less (2c)

in patients who have been untreated for many hours and in those wh[o] develop renal failure. In children or in adults who are admitted promptl[y] after onset of acidosis or coma, serum levels may be normal or low (se[e] figure 18-8 in Chapter 18). The average dosage of potassium *ion* in th[e] first 24 hours of therapy of our series of children in acidosis and coma [is] shown in table 20-II and the results of serial measurements of seru[m] potassium are illustrated in figure 20-4. The electrocardiographic chang[es] in a patient with hypokalemia and associated biochemical disturbance[s] are shown in figure 20-5.

In the case of phosphate the story is somewhat less complete but it [is] established that interruption of carbohydrate metabolism and acidosis [in] at least the isolated blood cell system is accompanied by conversion o[f] organic phosphates in cells into inorganic phosphates, increases in th[e] extracellular levels of the latter, and marked phosphaturia (15a-d). Th[e] serum inorganic phosphorus changes which occur during therapy are show[n] in figure 20-6.

3. The Simultaneous Repair of Potassium and Phosphorus Deficits

These losses of body potassium and phosphorus should be replaced, sin[ce] deficits of the former at least have been responsible for a fatal outcom[e] in otherwise adequately treated patients (13e). The infusion of buffere[d] potassium phosphate (KH_2PO_4 and K_2HPO_4) should be deferred, how[ever,] until it is established that renal output is good and function [is] adequate and until serum potassium levels have decreased to or belo[w] normal. The danger is, of course, potassium intoxication, since phospha[te] in these amounts has no specific toxicity. The height of the T-wave in le[ad] II can be used for ready detection of toxic levels of potassium if analys[es] by flame photometer are not available. Studies of both potassium and pho[s]phate levels reveal that in the patients who are responding satisfactori[ly] the serum concentrations of these ions fall to or below normal after two [to] four hours of therapy. Hence at the end of this interval 40 mEq, i.e. 3 [to] 4 gm. of the buffered potassium phosphate can be given safely by infusi[on] in 5 per cent glucose in the course of 1 to 2 hours to children above 5 yea[rs] of age and to adults. This amount if given slowly should not produce i[r]reversible cardiotoxicity in either group of patients. Administration ov[er] the recommended period provides margins of safety in that transfers in[to] cells or to the exterior as well as re-expansion of the body fluids will mini[mize] the rise in potassium.

The total amount of potassium to be used in 24 hours can be estimat[ed] from the studies of deficits in children and adults (2a, b, 16a-d). The[y] range from 3.2 to 11.7 mEq. per kg. of body weight (see table 19-II [in] Chapter 19). It is not necessary, however, to try to replace all of the

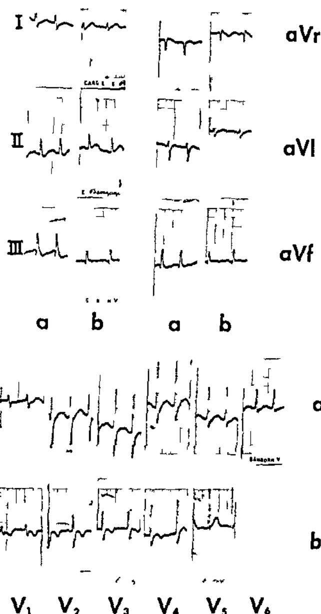


FIG 20-5 ECG AND SERUM SOLUTES DURING AND FOLLOWING THERAPY OF DIABETIC ACIDOSIS

Thi s 8 year-old m le d betic (D K) was admitted in coma Patient responded to treatment with the characteristic rise in serum total CO content and decrease in potassium Fourteen hours after admission the serum potassium was 1 6 the serum

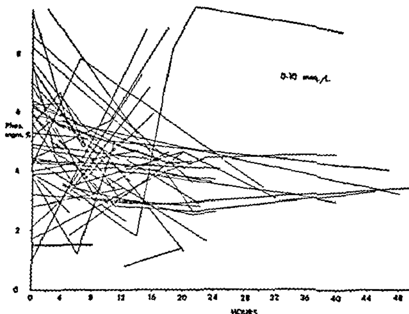


FIG 20-6 DECREASES IN SERUM INORGANIC PHOSPHORUS DURING THERAPY OF DIABETIC ACIDOSIS IN PATIENTS ENTERING HOSPITAL WITH SERUM TOTAL CO_2 CONTENT REDUCED TO 10 mEq PER LITER OR LESS (2c)

amounts in the first day Once oral intake has been started fruit juices and other beverages, potassium salts by mouth, 1.0 gm every 4 hours and ultimately foods will permit replenishment over a period of days An example of a balance study during a bout of acidosis in one of our juvenile diabetics treated in accord with this outline is shown in figure 20 7 (2a) It should be pointed out however that not all workers feel equally strongly about parenteral potassium therapy Hartmann *et al* (16e) have emphasized for example that recovery is so prompt that oral intake can be expected to make up the deficits

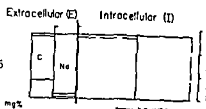
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total CO_2 content was 10.0 chloride was 107 and sodium was 128 mEq per liter The serum calcium and inorganic phosphorus were 10.2 and 1.79 mg per cent respectively The electrocardiogram taken at this time (series a in above) showed a rate of 136 QRS of 0.11 sec QT of 0.32 sec., and QTc of 0.49 sec Supraventricular tachycardia was present with probable nodal rhythm and wandering pacemaker The T waves were broad and flat in I aVr aVl and V2 V6 S T was depressed and T inverted in II and III

Two days later after serum K was 4.2 mEq and all other biochemical abnormalities had cleared the ECG showed sinus mechanism a reduction of the QRS interval to 0.07 sec and reversion of the S-T segments to normal configuration

Diabetic Acidosis (D C)
Before

Serum HCO_3 5 Na = 123
conc Cl 90 K = 65
meq per l Na – [HCO_3 + Cl] 28
Blood sugar = 582 NPN = 65 mg%



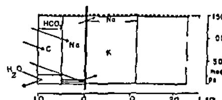
Therapy for 3 days

Insulin isotonic NaCl and 10% glucose i v KCl in milk p o

Exchanges	H_2O	Cl	Na	K
Given	12 6 l	1600 meq	1163 meq	616 meq
Excreted	15	1527	897	414
Retained E	0 3	73	146	– 19
Retained I	– 3 "		120	221

After

HCO_3 29 Na 139
Cl 98 K = 4 1
Na – [HCO_3 + Cl] 12
Sugar 167 NPN = 37



Interpretation Cl_E and Na_E retained without H_2O ketosis diminished and HCO_3 increased Na as well as K taken up into I

FIG 20 7 BALANCES OF WATER AND ELECTROLYTES AND RESTORATION OF BODY SOLUTES TO NORMAL CONCENTRATIONS DURING THERAPY OF DIABETIC ACIDOSIS

and related changes (2a)

1 Precautions during Potassium Therapy Potassium salts should never be injected rapidly or in undiluted form into tubing or into the vein because they can cause local spasm and pain (17a–c) and the concentrations reaching the heart may prove toxic (17d) If hyperkalemia and electrocardiographic or other evidences of cardiotoxicity appear all potassium intake should be stopped while continuing or increasing the administration of potassium free fluids The direct antagonism of intravenous calcium salts upon the cardiac asystole of potassium intoxication ($CaCl_2$ or Ca gluconate 1 0 gram as a 10 per cent solution intravenously) can be used in case of need (17e) This will not be necessary if the recommendations on dosage have been followed

V. The Use of Colloid Solutions

Impending or actual circulatory collapse secondary to the dehydration, sodium and chloride depletion and electrolyte disturbances also requires treatment (3 18a b) It should be emphasized that the blood pressure may be well maintained by means of vasoconstriction at the expense of diminished flow to the tissues We therefore routinely administer dextran within the first hour of therapy, 500 cc of a 6 per cent solution in saline to all cases of acidosis or coma irrespective of the status of the circulation Those in actual shock are given additional amounts There is adequate experimental evidence indicating that the use of colloid in salt depletion shock hastens recovery beyond the rate to be expected with sodium therapy alone (5c) Whole blood or plasma can also be used for this purpose, though typing and cross matching in the former and cross matching in the latter delay treatment Also dextran obviates the possibility of transmitting hepatitis

VI The Hazards and the Virtues of an Oral Intake

Some comment has already been made on the point that once overbreathing ceases many patients can be started on an oral intake 10 to 18 hours after admission provided the patient has not vomited in the interim (see table 20 V) This should be limited at first to water or tea lemonade or similar fluids with added sucrose and lactose (a total of 20 gm per hour per 200 cc in equal amounts) is palatable The infusions should be continued however until absorption is certain since vomiting may recur several hours later Many patients tolerate a one per cent solution of sodium chloride in bouillon or broth and this can be alternated hourly with the tea or other carbohydrate reinforced beverage After several hours and as the patient desires the intake can be broadened to include milk toast cereals etc On such regimens overbreathing ceases between the fifth and eleventh hours but may take longer (see 0–4 year old category in the 0 to 10 0 mEq group in table 20 V) It is usually possible to start a full diet on the day after admission This is highly desirable since it will help replenish the vitamins trace substances minerals such as calcium and magnesium and proteins

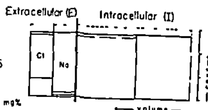
Summary

The prompt administration of insulin in adequate dosage is the undisputed essential of acidosis and coma therapy Infusions of sodium chloride and solutions of colloid (blood plasma dextran) replace extracellular deficits of these ions and of water and correct the accompanying circulatory collapse Overtreatment with the chloride ion can be avoided by limited use of physiologic saline or by judicious reliance upon hypotonic

Diabetic Acidosis (D C)

Before

Serum HCO_3 5, Na = 123
conc Cl = 90, K = 65
meq per l Na − [HCO_3 + Cl] = 28
Blood sugar = 582, NPN = 65 mg%



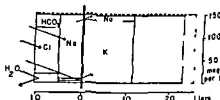
Therapy for 3 days

Insulin, isotonic NaCl and 10% glucose i v, KCl in milk p o

Exchanges	H_2O	Cl	Na	K
Given	12 6 liters	1600 meq	1163 meq	616 meq
Excreted	15	1527	897 "	414 "
Retained - E	0 3 "	73 "	146 "	− 19 "
Retained - I	− 3		120 "	221 "

After

HCO_3 = 29, Na = 139
Cl = 98, K = 41
Na − [HCO_3 + Cl] = 12
Sugar = 167, NPN = 37



Interpretation Cl_E and Na_E retained without H_2O, ketosis diminished and HCO_3 increased, Na as well as K taken up into I

FIG 20-7 BALANCES OF WATER AND ELECTROLYTES AND RESTORATION OF BODY SOLUTES TO NORMAL CONCENTRATIONS DURING THERAPY OF DIABETIC ACIDOSIS

This 16-year-old female juvenile diabetic was admitted in acidosis with hyperglycemia hyponatremia hypochloremia, hyperkalemia and azotemia During therapy extracellular water expanded slightly, cell water decreased, sodium was retained in the extracellular space and in cells, potassium in extracellular space and cells decreased and increased, respectively Lower diagram illustrates the direction of these and related changes (2a)

1. Precautions during Potassium Therapy. Potassium salts should never be injected rapidly or in undiluted form into tubing or into the vein because they can cause local spasm and pain (17a–c) and the concentrations reaching the heart may prove toxic (17d) If hyperkalemia and electrocardiographic or other evidences of cardiotoxicity appear, all potassium intake should be stopped while continuing or increasing the administration of potassium-free fluids The direct antagonism of intravenous calcium salts upon the cardiac asystole of potassium intoxication ($CaCl_2$ or Ca gluconate, 1 0 gram as a 10 per cent solution, intravenously) can be used in case of need (17e) This will not be necessary if the recommendations on dosage have been followed

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Summary

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TABLE 20 V

	Age Group	No of Patients	Average Age	Interval after Admission
	yr		*yr*	*hr*
A. Cessation of overbreathing				
0–10 0 mEq /L group	0–4	4	2 0	22 0
	4–8	1	6 2	6 0
	8–12	4	9 7	5 4
	12–16	8	13 9	8 0
10 1–15 0 mEq /L group	4–8	1	6 8	11 0
B Disappearance of acetonuria				
0–10 0 mEq /L group	0–4	24	2 2	14 6
	4–8	15	6 5	11 2
	8–12	33	9 9	15 8
	12–16	43	13 8	16 2
10 1–15 0 mEq /L group	0–4	6	2 5	25 9
	4–8	13	6 2	19 3
	8–12	15	9 6	11 9
	12–16	9	13 4	15 9
C. Resumption of oral intake				
0–10 0 mEq /L group	0–4	20	2 2	17 2
	4–8	12	6 2	14 2
	8–12	33	9 9	13 0
	12–16	46	13 7	12 4
10 1–15 0 mEq /L group	0–4	5	2 5	7 3
	4–8	7	6 2	9 0
	8–12	11	9 7	8 4
	12–16	5	13 0	5 0

replacement fluids, Ringer's lactate, or one-sixth molar sodium lactate However, the routine administration of alkalinizing solutions such as one-sixth molar lactate deprives the therapist of an important index of improvement and may result in inadvertent alkalosis The use of alkali should be reserved for seriously ill patients in whom marked decreases in pH are present

As the blood sugar and serum potassium and phosphate levels fall during therapy, glucose or fructose and buffered potassium phosphate should be added to the therapeutic regimen Oral intake should be resumed as promptly as possible but the recurrence of vomiting is a frequent prelude

to hypoglycemia unless the parenteral administration of glucose or fructose is resumed

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CHAPTER 21

Somatic Growth and Development of the Juvenile Diabetic. Endocrine Profiles

Although much has been said about the physical characteristics, growth and maturation of the diabetic child at the time of and following the onset of this disturbance in metabolism a number of the conclusions are contra dictory or controversial Furthermore Colwell has suggested that the course of all diabetes begins at birth even though the time at which it be comes manifest clinically does vary from patient to patient (1) It seems worthwhile therefore to see whether birth weight early development, body weight and height heart size skeletal maturation primary and secondary sex changes and endocrine indices are different in diabetic and nondia betic children

I Birth Weight and Early Development

It is now well established that adult females destined to become diabetic have babies who are large at birth (2a h) in addition to compiling a record of increased wastage of pregnancies by abortions premature deaths and stillbirths (2g i) (see also Chapter 25) Moreover W P U Jackson has introduced the concept of the prediabetic father (3a b) He has shown that adult males who ultimately develop diabetes also have offspring who at birth exceed the average body weight of children of fathers who ultimately prove to be nondiabetic In view of these observations and the knowledge that about 60 per cent of the diabetic children ultimately have a positive history of familial diabetes (see Chapter 7) should not their birth weights also be above average? The author has found no comments on this point and has therefore reviewed the Pittsburgh series The findings are shown in figure 21 1 The data indicate that the average birth weight of infants destined to become diabetic is no greater than that recorded for a nondia betic segment of our population (4a–c) Mirsky moreover has indicated to the author that in a series of more than 2000 big babies whom he has followed not one has developed diabetes (4b)

In figure 21 2 some information on the ages at which a group of our dia betic children began to raise the head sit crawl stand and walk is shown These do not appear to differ from the general experience in nondiabetic infants as cited in Nelson (4c)

II. Height and Weight at the Onset of Diabetes

Many observers have indicated that in their series the diabetic child was taller at the time diabetes was discovered and weighed less than his non diabetic contemporaries (5a–o) The belief that body height is increased has not been universal (5p, q), though agreement is more uniform in regard to body weight Thus, in the report on the Joslin series (5h) dated 1936 there were twice as many underweight as overweight diabetic girls, and the data from other clinics are in general agreement (5b, d, e, i n) Our findings are shown in figures 21-3 through 21-6 We have used the standards of Maresh (6a) based on serial studies of 128 children under the sponsorship of the *Child Research Council for purposes of comparison* These have

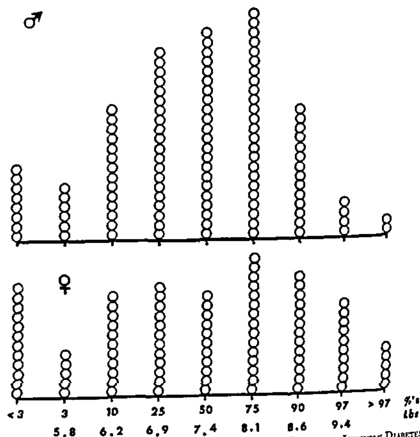


Fig. 21-1 Birth Weight of Infants Who Subsequently Developed Juvenile Diabetes ... to large

as those recorded in control groups

been made during the same decades covered by our own experience and encompass the same economic strata The children do differ, however, in their geographic and perhaps their ethnic origins Our data on body dimension percentiles (6b) are limited largely to children under treatment for diabetes and are presented later

A The Body Height and Weight of the Children's Hospital of Pittsburgh Series at the Onset of Diabetes

From figures 21-3 and 21-4 it is evident that the average heights of our diabetic population were often but not always less than those of the control groups, and that with the exception of the 5-year-olds there was no evidence of increased height This is true of the boys as well as of the girls irrespective of whether the data are expressed as averages or in terms of percentiles This does not mean of course, that occasional newly-discovered diabetics are not taller than the average but rather that such tall children are encountered with equal frequency in the nondiabetic and diabetic populations It is obvious, therefore, that previous conclusions to the contrary

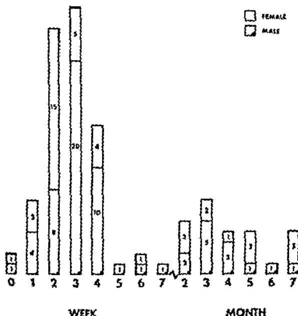


FIG 21-24 EARLY DEVELOPMENT OF INFANTS DESTINED TO BECOME JUVENILE DIABETICS
The age at which these infants held up their heads sat up crawled, stood up, and walked are comparable to those recorded in control infants (4b) Figures within columns refer to numbers of patients

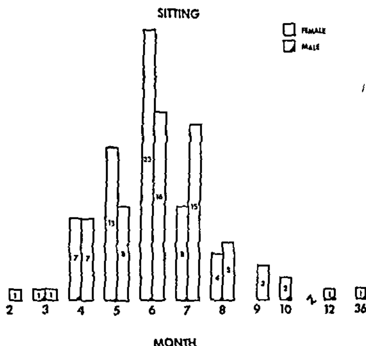


Fig 21-2B See Legend under Fig 21-2A

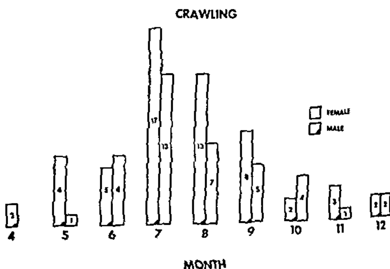


Fig 21-2C See Legend under Fig 21-2A

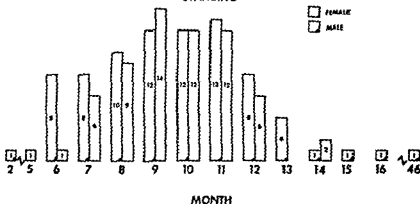


Fig 21-2D See Legend under Fig 21-2A

WALKING

FEMALE
MALE

6 7 8 9 10 11 12 13 14 15 16 17 18 19 24 48

MONTH

Fig 21-2E See Legend under Fig 21 2A

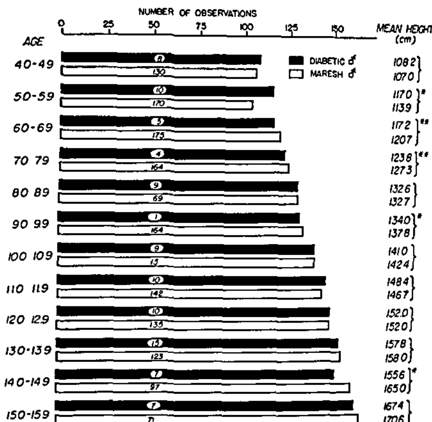


Fig 21 3 Average Height of Diabetic Boys at Time of Diagnosis

The earlier impression that diabetic children were taller than average at the onset of the disorder is not substantiated in our series Measurements at or within 2 months *following the diagnosis of diabetes generally revealed the mean body* height to be the same or less than that recorded in the Maresh control series of nondiabetics (6a) The 5 0 to 5 9 year age group is an exception Asterisks identify statistically significant differences with p values of <0 05 or <0 01 for * and ** respectively, and figures *within columns represent number of observations*

have been based upon comparisons with unsuitable control groups This certainly seems likely in the case of the earlier reports in which the standards of previous generations of children with differing economic, cultural and ethnic characteristics were employed (5a–n) It should be kept in mind that even today there is being recorded a progressive increase in the average height of our nondiabetic juvenile population

As indicated earlier, there has been less divergence of opinion concerning the lesser body weight at the time of the onset of diabetes Our own findings concur From figures 21-5 and 21-6 it is evident that on the average the diabetic children, both boys and girls, were underweight This con

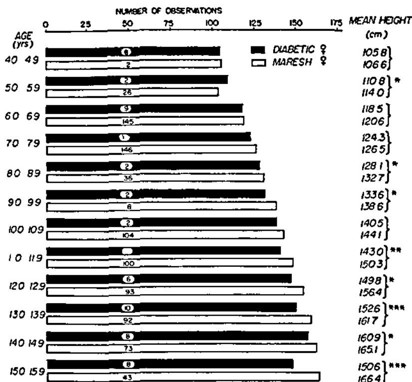


FIG 21-4 BODY HEIGHT AT OR SHORTLY AFTER DIAGNOS S OF JUVENILE DIABETES IN GIRLS As in the case of the diabetic boys the 5 0 to 5 9 year old group was taller than their contemporaries in the Maresh control series In the remainder the mean body he ght at the t me of diagnos s or w thin the succeed ng 2 months was either the same or less than that of the controls Aster sks (* and **) as in fig re 21-3 *** refers to p of less than 0 001

trasts of course with the frequent occurrence of increased body weight or obesity in the adult diabetic population (7a–d)

III Height and Weight Data and Body Dimensions Following 1 to 10 Years of Diabetes (Children's Hospital of Pittsburgh)

The data in table 21 I indicate that diabetic children under regular treatment in our clinic still show a tendency to being underweight and of decreased height compared to the Maresh control series (6a) However these are not large differences even though they are statistically significant. This is in keeping with the experience of others Thus Fischer Mackler

TABLE 21 I

Mean height and mean body weight of children with diabetes† present for intervals up to ten years in length compared with the data for non diabetic children as reported by Maresh

Age yrs	Diabetics			Non diabetics		
	Number	Mean	±S D	Number	Mean	±S D
			Height (boys)			
4, 5, 6	17	117 85	±11 38	473	114 50	±6 70
7, 8	29	126 76	± 6 42	333	130 03*	±5 28
9, 10	15	138 51	±10 01	315	140 01	±5 47
11, 12	16	148 51	±10 48	277	149 28	±6 13
13, 14	13	159 14	± 8 70	220	161 10	±7 51
15, 16	15	167 29	± 6 66	119	172 49*	±6 34
			Height (girls)			
4, 5, 6	15	110 53	±7 86	383	114 30	±7 51
7, 8	10	125 69	±3 17	282	129 48	±6 62
9, 10	14	138 48	±7 14	222	141 20	±7 29
11, 12	14	148 94	±7 64	193	153 27	±8 17
13, 14	18	154 12	±7 07	165	163 24*	±6 52
15, 16	8	159 64	±6 35	77	166 84*	±5 39
			Body weight (boys)			
4, 5, 6	18	22 64*	±6 13	473	20 15	±2 54
7, 8	29	25 58	±3 41	333	26 65	±3 15
9, 10	15	31 35	±5 95	315	32 09	±4 14
11, 12	17	36 50	±5 81	277	38 06	±5 59
13, 14	13	46 21	±8 11	220	47 61	±7 80
15, 16	15	52 74	±9 31	119	57 05*	±7 37
			Body weight (girls)			
4, 5, 6	17	19 79	±3 59	383	19 78	±3 01
7, 8	10	25 87	±4 09	282	26 29	±4 33
9, 10	14	31 46	±5 51	222	33 58	±6 44
11, 12	15	37 17	±6 94	193	41 69	±8 97
13, 14	19	42 87	±6 25	165	50 04*	±9 01
15, 16	8	55 68	±3 06	77	53 97	±8 83

† CHP series

* Differences are statistically significant

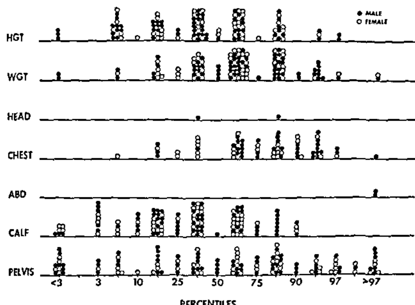


FIG 21 7 BODY DIMENSIONS OF DIABETIC CHILDREN IN TERMS OF PERCENTILES
In this group of diabetic children the individual measurements are fairly symmetrically distributed around the median point There are more children who are below the 50th percentile in height than above it in keeping with figures 21-3 and 21-4 Diabetes had been present up to 10 years with a mean duration of 3.39 years (CHP series)

Maresh's series (6a) In three of the age groups among the males a greater transverse diameter of the heart was accompanied by an increased internal diameter of the chest with resultant normal cardiothoracic ratios The difficulties of such measurement are well recognized (8g–o) However, they can be presumed to have been present to an equal degree in our diabetic and Maresh's control groups, since the same procedures were employed

V. Skeletal Development

A At the Onset of Diabetes

Again, as in the case of body height, some workers have felt that skeletal maturation was accelerated at the onset of juvenile diabetes (9a) Though there has been no systematic study reported in support or refutation of this view, it is now evident that when appropriate standards are used bone age is as a rule not advanced in these children Our findings (9b), in keeping with the latter opinion are presented in figures 21 8 and 21 9 They

TABLE 21 II

Comparison of transverse diameters of heart, internal diameters of chest and cardiothoracic ratios in diabetic and non diabetic children

Age yrs	Diabetics			Non-diabetics		
	Number	Mean	±S D	Number	Mean	±S D
	Transverse diameter of heart (boys)					
4 0- 6 9	18	8 89*	±0 70	473	8 42	±0 55
7 0- 8 9	29	9 18*	±0 74	333	8 90	±0 68
9 0-10 9	15	9 55	±0 86	315	9 22	±0 75
11 0-12 9	18	9 67	±1 09	277	9 67	±0 81
13 0-14 9	15	10 79*	±1 14	220	10 28	±0 90
15 0-16 9	15	10 75	±1 06	119	10 91	±0 85
	Internal diameter of chest (boys)					
4 0- 6 9	18	20 22*	±1 24	473	19 52	±0 98
7 0- 8 9	29	21 64*	±1 18	333	21 15	±1 03
9 0-10 9	15	22 79	±1 53	315	22 28	±1 23
11 0-12 9	18	24 04	±1 83	277	23 48	±1 41
13 0-14 9	15	26 57*	±1 99	220	25 36	±1 91
15 0-16 9	15	27 93	±2 24	119	26 95	±1 89
	Cardio-thoracic ratio (boys)					
4 0- 6 9	18	0 44	±0 04	472	0 43	
7 0- 8 9	29	0 42	±0 03	333	0 42	
9 0-10 9	15	0 42	±0 04	313	0 42	
11 0-12 9	18	0 40	±0 03	274	0 41	
13 0-14 9	15	0 41	±0 04	206	0 41	
15 0-16 9	15	0 39	±0 04	111	0 40	
	Transverse diameter of heart (girls)					
4 0- 6 9	17	8 48*	±0 58	383	8 16	±0 57
7 0- 8 9	10	9 00	±0 50	282	8 70	±0 64
9 0-10 9	14	9 24	±0 62	222	9 28	±0 80
11 0-12 9	15	10 01	±0 73	193	9 79	±0 90
13 0-14 9	19	9 93	±0 93	165	10 14	±0 86
15 0-16 9	9	11 02*	±0 85	77	10 31	±1 00
	Internal diameter of chest (girls)					
4 0- 6 9	17	19 26	±1 49	383	18 83	±1 06
7 0- 8 9	10	20 69	±1 08	282	20 37	±1 17
9 0-10 9	14	21 86	±1 24	222	21 95	±1 35
11 0-12 9	15	23 83	±1 62	193	23 46	±1 62
13 0-14 9	19	24 80	±1 74	165	24 91	±1 65
15 0-16 9	9	26 26	±1 26	77	25 58	±1 76

TABLE 21 II—*Continued*

Age yrs	Diabetics			Non-diabetics		
	Number	Mean	±S D	Number	Mean	±S D
	Cardio-thoracic ratio (girls)					
4 0–6 9	17	0 44	±0 03	383	0 43	
7 0–8 9	10	0 43	±0 01	283	0 43	
9 0–10 9	14	0 42	±0 03	220	0 42	
11 0–12 9	15	0 42	±0 03	189	0 42	
13 0–14 9	19	0 40	±0 03	157	0 41	
15 0–16 9	0	0 42	±0 03	74	0 40	

* Differences are statistically significant

have been compared with the standards of Greulich and Pyle (10a) and those of others (10b–d) derived from healthy children in communities with comparable economic ethnic, and geographic characteristics The conclusion is the same irrespective of whether the data are presented as a correlation of chronologic and bone age or as percentiles of the control group there is no evidence of accelerated osseous development In about one half of the children bone and chronologic ages are in excellent agreement (figure 21 8) falling between the fortieth and sixtieth percentiles (figure 21 9) In the remainder the bone age is retarded falling between the third and thirty fifth percentiles It is probable therefore that the original impression that bone age was accelerated resulted from inadequate sampling and a lack of suitable reference standards

B In Diabetic Children Under Therapy

The tendency for the distribution of bone ages to be shifted to the left at the onset of diabetes thereby indicating retardation is also evident after one to ten years of therapy (figure 21 9) It may be that this reflects inadequate control of diabetes a point difficult to refute or to establish directly The fact remains that the trend to retardation of skeletal maturation present at the onset persisted despite therapy Since it did not become more pronounced it may well represent an irreplaceable loss of a period of growth at the time the diabetes began (11a b)

VI Endocrine Patterns

A Sexual Maturation (Gonadotropins, Gonads and Adrenal Cortex)

The development of primary and secondary sex characteristics occurs under the influence of the gonadotropins and perhaps other tropic hormones of the pituitary which regulate the secretion of androgens and estrogens by

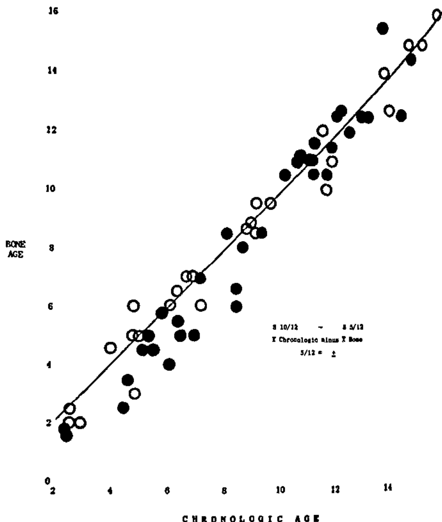


Fig 21-8 Bone Age in Relation to Chronologic Age

In many of these 63 diabetic children (solid circles refer to boys and open circles to girls) there is good agreement between the age of the patient and the bone age as estimated from the standards for nondiabetics (10a) The data have been plotted without regard to the duration of the diabetes The deviations just above and below the line which depicts identity cancel one another, the recorded mean difference of $-5/12$ of a year reflects the greater degrees of retardation up to 2 years in magnitude present in some of the children

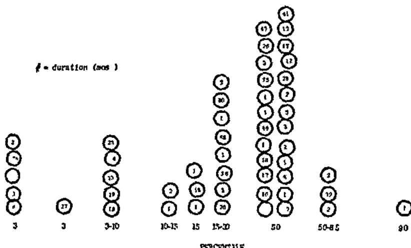


FIG 21 9 PERCENTILE DISTRIBUTION OF JUVENILE DIABETICS IN ACCORDANCE WITH BONE AGE

The numbers within the circles indicate the duration of diabetes in months in these 53 children With the exception of one patient at the 90th percentile and 3 others in the 50th to 85th percentile range the bone age of newly-discovered diabetic children is at or below the midpoint of the normal distribution curve for nondiabetics (10a) The erroneous conclusion of 3 decades ago (that bone development was generally accelerated in diabetics (9a)) was reached at a time when suitable reference standards were lacking Retardation of skeletal growth is probably present in a number of the long-standing diabetics

the gonads and the adrenal cortex (11a) Our data indicate that the diabetic in general moves into pubescence at the same time as the nondiabetic (11b) This is evident from the cross sectional survey of our children as shown in figures 21 10 and 21 11 However delays in the appearance of secondary sex hair in the male and female and of breast changes and menarche in the female do occur more often in diabetic than in nondiabetic children This is related either to a recent onset of the diabetes or to inadequate control of previously present diabetes Thus Wagner, White and Bogan (8e) in reviewing the data on 118 children with retardation of growth sufficient to categorize them as dwarfs i e a body height four inches below the average in the standards of Meredith, indicated that retardation was seen most often in pubescence with associated delay in sexual development Jackson and Kelly (8c) have commented that sexual maturation occurred normally in girls under adequate control whereas this was retarded with poor regulation They also noted that onset of diabetes at age 10 to 14 seemed to interfere with maturation. This observation that retardation and inadequate diabetic control were related is supported by

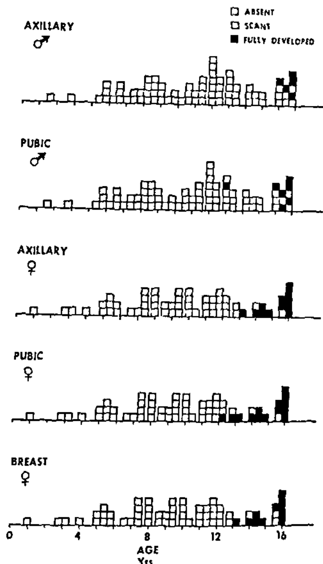


FIG 21-10 THE APPEARANCE OF SEX HAIR AND THE BREAST DEVELOPMENT IN JUVENILE DIABETICS

The age of appearance of axillary and pubic hair in male and female diabetics and female breast development are in keeping with the standards established in nondiabetic children (11b) It is to be noted that, as usual, sex hair appeared earlier in girls than in boys

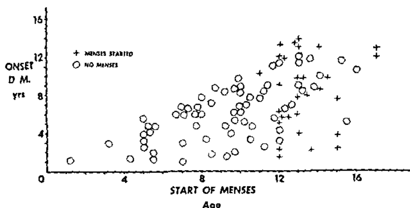


FIG 21 11 ONSET OF MENSTRUATION IN A GROUP OF DIABETIC GIRLS
Catamenia in female juvenile diabetics to be compared to the mean age of onset at 13½ years recorded in non-diabetics by Talbot *et al* (11b) Our observations are too limited to establish a delaying effect of a recent onset of diabetes on the initiation of menstruation as suggested by Jackson and Kelly (8c)

Bergqvist s endocrinologic data on 11 retarded diabetics (8d) Puberty was delayed to as late as 17½ years of age in the boys and menarche in the three girls occurred between the ages of 16 and 23 Urinary gonadotropins, estrogens, 17-ketosteroids, and 11-oxysteroids, and the serum protein bound iodine values were not unusual

In table 21-III and figure 21 12, respectively, we have plotted the excretion of gonadotropins and 17-ketosteroids in diabetic children of various age groups in urines obtained when the patients were under satisfactory control (12a) These fall within our range of normal Others have reported a preponderance of above normal or below normal values for urinary 17-ketosteroids (12b–g) some and perhaps all of the former may be attributable to increased adrenocortical activity as a part of subclinical ketosis or acidosis (see Chapter 19) Izzo and Eilers (12h) found that in their group of diabetics the low normal or below normal basal excretion of 17 ketosteroids increased following cortisone to a greater extent than in controls This response is unexplained but is akin to that of cancer patients under the same circumstances (12i)

The urinary excretion of corticoids and of formaldehydogenic steroids has also been reported to be decreased in some diabetics (12j–l)

B Other Evidences of Adrenocortical Activity in the Regulated Diabetic the Serum Levels of Corticosteroids

In Chapter 19 it was indicated that diabetics in general show a level of serum corticosteroids which is slightly greater than that observed in non-

TABLE 21 III

Urinary excretion of gonadotropins in juvenile and formerly juvenile diabetics

Pt	Age yrs	Sex	Mouse Units				
			6 6	13	26	53	106
I Y	11	F	–	–	–	–	–
L S	12	F	+	–	–	–	–
C S	12	F	+	–	–	–	–
S C	14	F	+	+	±	–	–
B S	15	F	–	–	–	–	–
M F	16	F	+	±	–	–	–
A M	16	M	–	–	–	–	–
R S	17	F	–	–	–	–	–
M F	18	F	+	–	–	–	–
R T	19	F	–	–	–	–	–
J B	24	F	–	–	–	–	–

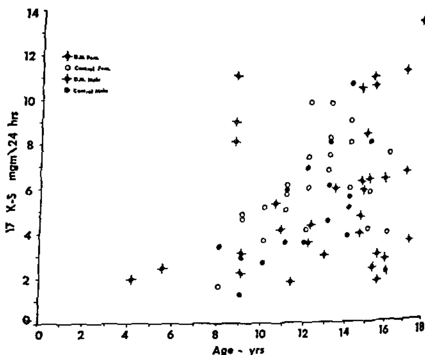


Fig 21 12 Urinary Excretion of 17 Ketosteroids in Regulated Diabetics
The values in diabetics (circles with superimposed cross) fall within the range of normal established in this laboratory for healthy nondiabetic children by the method of Holtorff and Koch

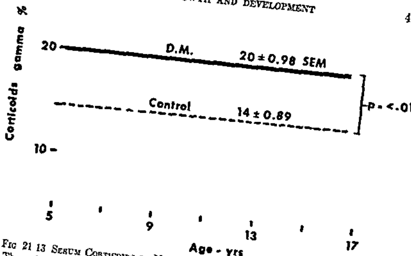


Fig 21 13 Serum Corticoids in Nonketotic and Nonacidotic Juvenile Diabetics These diabetics selected at random from our series were found to have serum corticoid levels equal to or slightly greater than those observed in controls (data of Klein *et al* (13a b))

PBI
γ %
51 ± 1.0 DIABETIC
47 ± 0.8 NON-DIABETIC
DIABETIC MALES
DIABETIC FEMALES
NON DIABETIC MALES
NON DIABETIC FEMALES
AGE – YEARS

Fig 21-14 Comparable Levels of Serum Protein-Bound Iodine in Diabetic and Nondiabetic Children (14a)

diabetic controls and that acidosis greatly increases this difference (13a b) The distribution of values in children under presumably adequate control is shown in figure 21 13

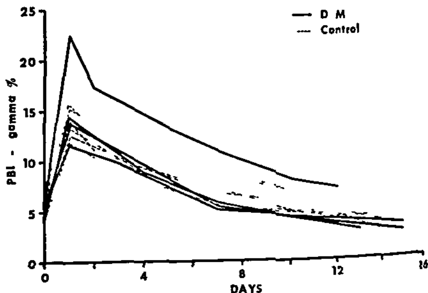
C Thyroid Function in the Diabetic as Indicated by Serum Protein Bound Iodine Levels

Our data (14a) indicate that the serum protein bound iodine concentrations which under appropriate circumstances accurately reflect thyroid activity (14b) are the same in diabetic and nondiabetic children in the various age groups (figure 21 14) and that the dip in the distribution curve which appears at the time of puberty in the control group is also evident in the diabetics

Diabetic children respond to exogenous thyroxin with serum protein bound iodine changes comparable to those seen in nondiabetic control children (figure 21 15) (14c)

D Parathyroid Activity as Reflected in the Serum Levels of Calcium and Phosphorus

There is no evidence that these serum constituents are regularly altered in diabetic children (see Chapter 17) though the levels of serum phos



l d lines)
mparable
the same

phorus fluctuate through a greater range of values than in normals (see Chapters 8 through 12 and 18) These describe the changes in this electrolyte with increases and decreases in carbohydrate disposal induced by glucose, insulin, epinephrine, glucagon, and acidosis and coma

Summary

The early development of the child who ultimately becomes diabetic is comparable to that of his nondiabetic confreres The initial reports of increased height and accelerated bone age at the onset of diabetes have not been borne out upon comparison with suitable control groups of nondiabetics, body weight is usually below normal The retardation in height and weight persists in general after therapy has been instituted, probably because growth periods have been lost Occasional delays in pubescence and adolescence are encountered, but indices of gonadotropin output, thyroid activity, and adrenocortical secretion are not strikingly different from values encountered in nondiabetic children

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CHAPTER 22

The Personality, Emotions, Intelligence, and Scholastic Performance of Diabetic Patients; the Role of Emotions in Diabetic Regulation

In any large juvenile diabetic service it is amazing to see the degree of real or apparent compliance with the regimen that is imposed It is reasonable to ask whether in this emphasis upon the regulation of the metabolic aspects of diabetes the individuality of the patient is being suppressed to the point that resentment, negativistic behavior, hostility, etc develop There certainly are problem patients among the diabetic group, but they are a distinct minority Why is this group not larger, especially among the adolescents and teen-agers who often rebel bitterly at conventions and restrictions even when they do not have diabetes(1a, b)? Do diabetics as a group begin with an emotional pattern which makes them welcome the security of the regimentation of diabetes, or do they really harbor resentment or turmoil which is effectively concealed most of the time but becomes manifest in episodes of ketonuria, glycosuria, and impairment of diabetic regulation? Are these patients of average intelligence? The answers to these and related questions cannot be complete at this time but certain general patterns can be indicated from the limited studies available

I. The Personality and Emotions of Adult and Juvenile Diabetics

A Personality Profiles of Adult Diabetics

Flanders Dunbar and her colleagues (1c d) have summarized the predominant personality features of a group of several hundred adult hospital diabetics She believes that out of this survey there emerges a pattern of traits which though it may not be uniformly present in individual diabetics, does set these patients apart from other psychosomatic diagnostic groups

She points out that the childhood of the diabetic whose carbohydrate disorder develops after reaching maturity is frequently characterized by a marked conflict between hatred of the parents and submission to them Temper tantrums, phobias, and nightmares are present more frequently than in groups of patients with hypertensive cardiovascular disease or with

myocardial infarction These children who later as adults develop diabetes have a better educational record than that of the general population but there is a high frequency of "nervous breakdowns" in college In the interval prior to the onset or the diagnosis of diabetes there is often a long period of 'wear and tear", i e hard work, struggle with family and spouse recognized or unrecognized homosexual conflict, and dietary indiscretion The health record itself is good prior to the diabetes

After diabetes has developed, the patient tends to dissipate his energy in innumerable minor tasks and concerns He has difficulty following a consistent course of action because of vacillation and indecisiveness and cannot manage interpersonal relationships effectively Despite a higher educational background he remains at lower vocational and income levels The males tend to remain unmarried In those who marry, both the males and females have relatively few children The divorce rate is low but there is a high incidence of frequent separations and living apart The struggle with the parents in childhood is now transferred into the marital relationship Sexual adjustment is usually inadequate and marked by anxiety A homosexual trend can be detected and the venereal disease rate is low These patients tend to be nervous, depressed, suspicious, and paranoid as a group The illness is often used as an alibi (1c, d)

In contrast to Dunbar's findings Lisansky (1e), after comparing 100 adult epileptics with 10 adult diabetics, reached the conclusion that there is no typical personality picture which characterizes the diabetic group and distinguishes it from other sick or neurotic groups

B Psychologic and Psychiatric Studies in Diabetic Children

There have been a number of attempts in the past two decades to characterize the emotional and personality patterns of juvenile diabetics In general these have not revealed any unusual deviations from control groups nor have constellations been identified However, Daniels (2a) reporting on a series of comprehensive interviews on 23 diabetic patients ranging in age between 15 and 55 years, indicated that all revealed material of interest to the psychiatrist The manifestations included reactive depres to deal with constitutional predisposition but its probable importance was emphasized

In the studies of Shirley and Greer (2b) on 155 diabetic children in Iowa the roles of an unwholesome home environment, faulty parental attitudes, and an unsound economic basis in personality disturbances such as feelings of inferiority and inadequacy and retreat in physical complaints were emphasized Twenty two of the children came from broken homes and more than one fifth of the parents were uncooperative, indifferent, or in

tellectually inadequate while others were too solicitous and too protective Though only five of the children were classified as major eating problems, the diet and insulin represented a financial burden in almost one-half of the families and the majority of these were on public assistance These authors point out however that their study was based on findings in a lower economic or actually indigent class

The group of 49 children studied in Buffalo by McGavin *et al* (2c) was more representative of their nondiabetic confreres A few of the children deviated grossly from normal in personality traits but this was not felt to be an excessive number for such a small unselected group In 32 of the children with less major maladjustments it was felt that physical and intellectual defects and social and economic problems played causative or important contributory roles It was the impression of these workers that the earlier the onset of the diabetes the better the emotional adjustment

Brown and Thompson (2d) also concluded after studying 60 juvenile diabetics by means of the Woodworth-Cady psychoneurotic inventory that they closely resembled their nondiabetic Minnesota confreres

Another study of the personalities of a moderately large group of diabetic children, 114 in all by Loughlin and Mosenthal (2e) revealed that three fifths were normal *i e* in terms of a sense of personal security, acceptance by their group, interest in activities, and attitudes toward body functions In the remainder abnormalities in one or more respects were encountered consisting of true neuroses or personality disturbances with unduly aggressive or retiring, devil may care, immature, or escapist attitudes

Fischer and Dolger's group of 34 private and nine clinic patients were observed for 10 to 20 years (2f) Minor behavior disturbances were frequent and the authors felt many of these were produced or aggravated by the diabetic regimen However, the home, the school, and the degree of economic security all appeared to influence the reaction of the diabetic child to his disease The patients in the better economic group with better home and school environments and higher intelligence ratings made a more satisfactory adjustment to the diabetes In those with personality disturbances in either group maturity usually brought an improvement Serious psychopathic behavior was encountered in three patients

Bruch (2g) after observation of 37 diabetic children concluded that there was no uniform psychologic picture and no evidence of a constellation of findings of the type seen in obese children where an overpoweringly possessive mother lives through her children, overfeeding them, being overprotective, etc She felt that diabetes re-enforces existing problems and that in those with an early onset an unusually submissive attitude was apt to develop The children varied in personality from happy, outgoing,

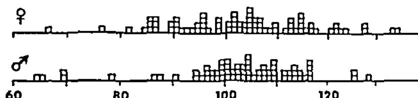


FIG 22 1 THE INTELLIGENCE OF JUVENILE DIABETICS
In these 68 diabetic boys and 75 diabetic girls in our series the intelligence as measured by the Binet-Simon or related procedures (some of them as group tests) is only sporadically retarded

ministered in the public school systems of Pittsburgh and the adjoining communities, and on measurements made in applying the Minnesota Multiphasic Personality Inventory to adolescent and overage diabetics The distribution appears quite normal (figure 22 1) Their scholastic performance appears to be about average as indicated by progress in school their grades, and the results of achievement tests

The marked incidence of mental retardation in some series as in those of Teagarden (5a) and of Boulin (5b) undoubtedly reflects a combination of nonrepresentative selection poor genetic background, and inadequate growth and development This may also be true in the series reported by Shirley and Greer (2b) in which the 155 diabetic children had an average intelligence slightly below Termaine's 1000 unselected children though 18 were mentally retarded including 11 in the borderline and seven in the moron categories In most series, however, as in McGavin's (2c) and Brown and Thompson's (2d) in which the diabetics were no brighter and no duller than the nondiabetics, in the Fischer and Dolger study (2f) in which the Stanford Binet test yielded the same result in 24 diabetics as in a group of comparable controls in those of Wagner *et al* (5c) where the I Q ranged ... rted by

In some of the older series it has been pointed out that diabetics com pleted more years of formal schooling (6a) This *per se* cannot be taken *as indicative of superior intellectual endowment* since any physical ab normality is accompanied by a greater impetus toward schooling as a possible help in overcoming economic and social handicaps, and by sym pathy, encouragement and understanding on ... of parents teach ers, and friends Grec ... e on manual ... also account for the higher ... rity of ... l in some dia betics (6b)

Sporadic instanc ... l children are sometimes ... *shocks* ...) incurred in

seeking "perfect" control, but convulsive seizures of the grand mal type may also occur during less restrictive regimens

III. Effects of Emotions on the Regulation of Diabetes

Acute or chronic emotional disturbances can have an effect on diabetic control as deleterious as that associated with infection, starvation, carbohydrate deprivation, immobilization, or chronic overinsulinization The studies of Hinkle, Wolf, and associates have provided quantitative support for this view They have demonstrated that emotional disturbances in diabetics can produce ketosis and increased glycosuria which clear with removal of the stress (7a–c) Subsequently they pointed out that this appears to be an exaggeration of a reaction which also occurs in nondiabetics (7d) Associated changes include decreases or alterations in blood sugar and a water diuresis accompanied by increased excretion of ketone bodies and chlorides (7e–h) These reactions have been observed in diabetics and nondiabetics in the course of obvious rebellions but they may also occur as unconscious reactions to conflicts with parents, to threats of examinations, to impending surgical operations, etc

Furthermore, Hinkle *et al* (3d, 7a–c) and others (8a–d) have demonstrated that emotional disturbances can result in a loss of diabetic regulation, ketoacidosis, and coma The accompanying losses of water and electrolytes in the stress diuresis further accelerate the deficits which occur in acidosis and coma as a consequence of the uncontrolled glycosuria and the discharge of adrenocortical oxysteroids cited in Chapter 19

IV. Can Diabetes Be Precipitated by Emotional Disturbances?

The recognition of the fact that emotional disturbances can aggravate pre-existing diabetes makes it logical to ask whether they may also bring a latent diabetes to a level of clinical manifestations Such instances do indeed occur (9a–c) However, there is no extensive support for the suggestion that diabetes actually originates as a result of such stress (1a, 2g, 9d–f) Thus Gendel and Benjamin (9g) in a study of 44 cases from World War II concluded that in no case was it possible to prove a direct causal relation between the stress incident to military service and subsequent development of permanent diabetes This however only emphasizes the point that one person's strain is another's security, and that the answer to the question of what is a suitable stress which may be productive of diabetes is undoubtedly a highly individual matter (9h, i)

There is no evidence that the incidence of diabetes is increased in schizophrenia nor in any other psychosis, though they may, of course, be present in the same patient (9j–l) However, in seeking precipitating causes of diabetes it is important to keep in mind Mirsky's admonition that the past

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CHAPTER 23

Vascular Diseases in the Diabetic and Other Ocular and Renal Changes

It has been noted repeatedly that vascular complications have replaced coma as the leading cause of death in diabetics The mortality statistics indicate that in the older patients these are largely attributable to sclerosis of the larger arteries and in younger patients to involvement of the smaller vessels, especially those of the eyes and kidneys

I. Atherosclerosis in Relation to Other Vascular Changes in Diabetes

For many years it has been recognized that the atherosclerotic and arteriosclerotic changes which develop in the later years in the nondiabetic population (1a) appear earlier and more frequently in the diabetics (1b) There is in addition a greater degree of arteriosclerosis of wider distribution, a higher incidence of coronary occlusion, and a change from the usual sex distribution (3 or 4 males to 1 female) to a 1 1 ratio (1c–s) There is evidence that heredity plays a factor in that there is a higher incidence of a family history of hypertension in the hypertensive diabetics than in the nonhypertensives (2a–c)

The etiology of arteriosclerosis in the diabetic and in the nondiabetic remains obscure The studies of Keys and of others in nondiabetic populations in various parts of the world indicate that the higher the total caloric intake and the proportion of fat the more likely the occurrence of vascular disease The cholesterol content of the diet *per se* is probably unimportant (3a–f). This is in keeping with the finding that human tissues and blood vessels themselves are capable of synthesizing lipids (4a–d) There is evidence that S_f 12–100 lipoprotein molecules are present in greater concentrations in atherosclerosis (5a) with higher beta and lower alpha lipoprotein fractions (5b–h), but it is not certain that *these or other lipid fractions* are altered in diabetics who do not have this complication (6a, b) At present therefore we are left with the knowledge that the atherosclerotic changes which begin virtually at birth in all human beings (7a) run an accelerated and accentuated course in the diabetic However, in our series of juvenile diabetics we have yet to see peripheral arteriosclerosis of the ex-

frequency of the type seen in older diabetics with infection, osteomyelitis or gangrene (7b).

With the survival of juvenile diabetics into young adulthood following the advent of insulin it soon became evident that vascular changes were also especially apt to develop in this age group (8a–p). In some of the earlier reports the appearance of lesions in the eye, albuminuria and an increased incidence of vessel calcification were attributed to accelerated arteriosclerosis. Further study has revealed, however, that the lesions in the eyes and kidneys differ histologically from the so-called degenerative changes of old age and has led to the use of terms such as angiopathy, retinopathy and nephropathy in referring to these processes.

II Retinopathy in Diabetes Mellitus

Dolger was the first to point out that after 20 or 25 years all or virtually all diabetics developed retinal vascular changes in various degrees (9a, b). In the earliest phase these appear to consist of small deep hemorrhages which may then progress to punctate hemorrhages, especially in the macular region. Hard yellowish white exudates may appear and coalesce. The veins dilate and become beaded. Hemorrhages into the vitreous and new blood vessel formation may lead to retinal detachment and blindness (figure 23 1). In young diabetics the venous changes may occur as the first sign of retinopathy. The occurrence rate is as high as 80 per cent after 15 or more years of diabetes (9c) though a lower incidence has been reported (9d). These changes are not confined to juvenile diabetics. Perhaps this fact led to the original view that they represented a form of accelerated arteriosclerosis.

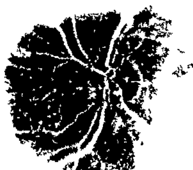


FIG 23 1 EXTENSIVE RETINOPATHY IN A JUVENILE DIABETIC
This 29-year-old white male developed diabetes at the age of 11. Fundus shows many microaneurysms (photograph kindly supplied by J. Finn Jr. M.D.)

4 *Histologic Findings*

In 1950 Friedenwald (10a–d) demonstrated by means of full thickness *retinal preparations that the lesion in the fundus resembled the vascular* changes described by Kimmelstiel and Wilson (10e) in the kidneys of diabetics The cherry spots or small deep hemorrhages *are not extravasations* initially but rather saccular or at times fusiform aneurysmal dilatations of the retinal arterioles with subsequent deposition of hyaline material and scarring They are not athero or arteriosclerotic changes (10f m) In our series as in others these changes were seen only infre*quently in juveniles with diabetes of less than 15 years duration (10n)*

III Diabetic Nephropathy

The appearance of albuminuria not explicable by urinary tract infection or of some other benign or reversible origin such as the orthostatic type or *that seen with certain drug* is an extremely ominous sign in diabetes Distressing as visual impairment may be it at least does not of itself present the same jeopardy to life Fortunately the incidence of nephropathy is not as high as that of retinopathy (8a c h i j l m 9c 11a–d) and usually its course is not rapid In too many patients however the originally minor degree of albuminuria ultimately becomes so profuse that the development of a full nephrotic syndrome becomes almost inevitable The *heavy loss of protein in the urine* is usually accompanied by casts and is in time followed by the other features of the complete syndrome i e by decreases in serum albumin edema and hypercholesterolemia Renal failure and moderate azotemia hypertension and retinopathy then develop to give the clinical picture first described by Kimmelstiel and Wilson (10e) *It should be recognized however that incomplete forms of* the syndrome occur and that the course is at times modified thus if sodium restriction or other measures are effective in preventing or correcting the retention of this electrolyte the onset of edema is deferred prevented or reversed

A *Histopathology of the Kimmelstiel Wilson Changes and Their Relation to Diabetes*

As in the case of the retinal lesions in juvenile diabetes this nephropathy

zation of the center of the glomerulus or of a lobule with broadening of the intercapillary connective tissue and the studies of McManus (11c) made it clear that in these patients at least arteriosclerosis was not the basic pathologic process In subsequent reports it became evident that the histologic lesion could occur without signs or symptoms in nondiabetics and diabetics and that the clinical syndrome

could develop in diabetics who at postmortem examination failed to show the characteristic lesion (12a–k) The first of these observations did not prove too troublesome, since the morphologic changes might not have been marked nor of sufficient duration to produce clinical findings The second raised the question of alternative etiologies of the nephrotic syndrome seen in diabetes

B Known Causes of the Nephrotic Syndrome

At present there are several recognized causes or, perhaps a better way of expressing it, diseases in the course of which the nephrotic syndrome may occur The well-documented observations of Bloom and Seegal (13a) in 1946 established that at that time the disease in which this syndrome developed most frequently was glomerulonephritis In their report and in others it has been pointed out that the nephrotic syndrome also occurs as the so called lipoid nephrosis of childhood in the Kimmelstiel-Wilson syndrome of diabetes referred to above in amyloidosis, syphilis, intoxication with drugs such as sulfonamides and anticonvulsants pyelonephritis, lupus erythematosus disseminatus and in renal vein thrombosis (13a–i) Recently Rifkin and associates have pointed out the value of demonstrating doubly refractile fatty cells or casts in fresh acid urine which stain lightly with Sudan III or IV in differentiating intercapillary glomerulosclerosis from other renal lesions (13j, k)

C Results of Needle Biopsies of the Kidney in Diabetic Patients

The advent of needle biopsies of the kidney now permits antemortem inspection of glomerular and tubular changes It is too soon to make a definitive statement but the observations by Kark and by others and our own small series of observations suggest that lupus is increasing as a concomitant of the nephrotic syndrome (14a–c) This probably reflects the higher incidence of disseminated lupus on medical services in general Use of the biopsy technique has further established that the clinical manifestations given in the original descriptions of the Kimmelstiel Wilson syndrome may occur in the presence of nephrosclerosis or pyelonephritis without evidence of intercapillary glomerulosclerosis Our findings are shown in table 23 I and others have reached the same conclusion (14d)

D Cardiovascular Renal and ECG Findings in Selected and Unselected Groups of our Juvenile Diabetics

Blood pressure, urinary and related findings in a group of patients known to have had juvenile diabetes for ten to 20 years are summarized in table 23 II, including those found to have nephropathy or retinopathy (15g, h) Profuse albuminuria or a frank nephrotic syndrome has only rarely oc-

TABLE 23 I

Findings on renal biopsy in patients with profuse albuminuria or frank nephrotic syndrome

Patient	Sex	Age	Diabetes	Duration yrs	Biopsy Findings
A D	Male	34	Yes	15	Arteriolar nephrosclerosis
D G	Male	39	Yes	19	Hyalinization of glomeruli compatible with *intercapillary glomerulosclerosis*
W C	Male	32	Yes	14	Intercapillary glomerulosclerosis arteriolar nephrosclerosis, hyalinization of glomeruli
G P	Male	38	No		Arteriolar nephrosclerosis
G W	Male	49	No		Hyaline droplets
N A	Female	33	No		Undiagnosed disease of kidney, chronic pyelonephritis, hyalinization of glomeruli, sclerosis of renal arterioles
C A	Male				Pyelonephritis, acute and chronic focal
A Y	Male	36	No		Subacute glomerulonephritis—nephrotic stage
E M	Female	26	No		'Wire loop" changes in glomeruli
J G	Female	32	No		Membranous glomerulonephritis or lupus erythematosus
M M	Male	24	No		Insufficient for diagnosis
J K	Male	26	No		Insufficient for diagnosis

curred thus far in our series (one example is shown in figure 23 2) but this merely reflects the fact that the number of our cases is limited and the follow up period relatively short

IV. Retinopathy and Nephropathy: Concomitants or Complications of Diabetes?

A number of clinics have reported that the frequency of retinopathy (15a–f) and of nephropathy (16a–l) was higher in the less well controlled members of their diabetic population Some feel that it is the duration of the diabetes rather than its severity or the degree of control that determines the incidence of retinopathy and nephropathy (8m, 9a, b, 17a–g) Others are undecided as to the role of unregulated diabetes in these manifestations (18a, b)

In any discussion of this question it should be emphasized, as others have done, that the Kimmelstiel Wilson syndrome occurs far more often in relatively mild diabetes as indicated by a relatively small insulin requirement and infrequency of diabetic acidosis or coma (19a, b), and that the vascular lesions may appear before the diabetes develops (20a–c) Perhaps the most telling argument of all, however, is recognition of the

fact that the incidence of these changes is extremely high even in the clinics operated with the most rigid control criteria The results in these clinics can hardly be offered as evidence of the benefits of a strict regimen in preventing retinopathy and nephropathy The author does wish to make clear, however, that he agrees that the symptoms of diabetes should be controlled as effectively as possible (see Chapters 14 through 16), and that in our clinic we are delighted with normoglycemia but unwilling to subject the patients to the risks of repeated insulin shocks to attain this degree of control

Perhaps the most pernicious effect of the view that strict regimentation prevents the vascular complications of juvenile or other long-term diabetes is the distraction of the interest of clinicians and investigators from studies of alternative views It is quite possible that these eventualities are manifestations of the disordered metabolic pattern of the diabetic but mediated through more subtle or intricate factors than simple hyperglycemia and glycosuria Is it another reflection of an inherited susceptibility to vascular diseases? The higher incidence of hypertension in diabetic families cited earlier is in keeping with this possibility (2a–c) Recently Ditzel and Rooth (20d) have suggested that the micro-angiopathy in diabetes mellitus may represent a pathophysiologic vasomotor reaction to variations in oxygen and carbon dioxide tension akin to that seen in retrolental fibroplasia

V. Therapy of Arteriosclerosis, Retinopathy, and Nephropathy in the Diabetic

The diabetes should be regulated as completely as possible, but the clinician must not delude himself that this will necessarily prevent, minimize or resolve any of these concomitants or complications in a particular diabetic

A Arteriosclerosis and Retinopathy

From the viewpoint of atherosclerosis, control of obesity and interdiction of excessive calorie and fat intake, and of certain types of fat in particular, are in order (3a–f, 20e–j) Insofar as retinopathy is concerned, all therapeutic trials based on the use of rutin (21a–c), adrenocortical products and B-vitamins (21d), testosterone (21e), and other agents (21f) have failed to date Attempts to relate the retinopathy to levels of serum proteins, lipoprotein, protein-bound carbohydrate (mucopolysaccharide complexes) or cholesterol (22a, b), or to vitamin B_{12} concentrations (22c), have been without success or have shown only occasional correlations However, insofar as the nephropathy is concerned recent studies (see be-

TABLE 23 II

Insulin requirement and cardiovascular renal findings in a group of juvenile diabetics (CHP series) in whom diabetes had been present 10 to 20 years

Patient	Age yr	Sex	Duration yr	Current Insulin Dosage	Blood Pressure	Fundi*	Urine Albumin†	NPN mg %	PSP (2 hr) %	Chest Film	ECG
W S	15 5	M	10 1	P 18 R 30	146/78	O	O	48		neg	
R M	15 9	M	10 3	P 15 R 30	118/70	O	T 1+	39			
M M	13 3	M	10 5	P 10 R 20	106/80	O	O	39	67	neg	neg
F S	15 5	M	10 5	P 22 R 47	138/90	O	T	32			
M A	15	F	10 5	P 70 R 36	134/90	O	O	35		neg	neg
J S	13 2	M	10 5	P 34 R 16 —O—12	106/82	O	T	34		neg	neg
D K	14 7	M	10 6	P 17 R 45	120/75	O	O	37–41	60	neg	neg
B S	13 5	F	10 8	P 11 R 34	100/50	O	O	26	40	neg	neg
J S	12 1	F	11 1	P 10 R 26	115/75	O	1+	33			
B B	15	F	11 1	P 24 R 40	110/75	O	O 1+	30	70	neg	
B D	16	F	11 1	L 28 Reg 68	112/74	O	T 1+	40			
R O	17	M	11 6	P 25 R 50	120/80	H	1+	33	62		
K S	15 7	M	11 6	P 10 R 40	120/78	O	T	31		neg	neg
C D	14 1	F	11 7	P 15 R 32	98/65	O	T 1+	32	61	neg	neg
W S	15 8	M	12	P 12 R 30	130/80	O	O 1+	26		neg	
B B	18	F	12	P 25 R 45	105/80	A	T	32	61		neg
M D	16	F	12 1	NPH 65 R 10	120/65	O	T 1+	35	65		neg
M C	15 3	M	12 2	L 40	110/90	O	1+	37		neg	
J T	13 8	M	12 3	P 14 R 45	115/100		O T	37		neg	
T T	20 3	M	12 5	P 15 R 45	124/66	H	O	31	52		
W W	14 1	M	12 5	P 8 R 37	138/100		O	34	68		neg
R D	15	M	12 6	P 13 R 10 —O 8			O T	38		neg	

J B	15 8	M	12 7	P 27 R 60	116/78	O	1+	37	65	neg	neg
I M	13 6	F	12 8	P 17 R 66	110/80	O	O 1+	28		neg	
J F	17 1	M	12 9	P 22 R 56	100/55	H	O	40	65		neg
V H	15 9	M	13 7	P 40 R 15	112/60	O	O	35		hilar glands	neg
J D	15	F	13 8	P 10 R 20	100/70	O	T	27		neg	
M H	15	F	14	P 18 R 28	110/40	O	O	33		neg	
W C ‡	32	M	14	P 20 R 25	180/110		T 4+	52–98	20	neg	
W N	25	F	14	NPH 25	130/95	B	200	39–49		neg	
F W	17 5	M	14 7	L 60			T§	33	64		neg
J D	23	F	15	P 30 R 20	100/60	H A	T	27	55		neg
A D	34	M	15	R 5	140/80		200	85			neg
R A B ‡	25	M	15	P 40 R 20	180/120	H A	2+ 3+	36–89	50	neg	L vent prepond
S D ‡	30	M	15	NPH 50	130/90	O	40–400	33 100	70		Cor insuff
C W	19 7	F	15 1	P 25 R 45			O	31			neg
T J	25 1	M	15 1	P 35 R 65	125/85	H	T	36	78		
J I ‡	18	M	16	P 14 R 42	168/120	T H A	1+	158 191		neg	
C R	18 7	F	16 1	P 20 R 40	100/75	H	T	31	67		neg
M S	19	F	17	NPH 34 R 10	98/60	A	T				
G S	21 3	M	17 1	P 15 R 30	110/40	O	O	45	34		neg
J B	25	F	19	P 10 R 15	110/70	O	O	27		neg	neg
D G ‡	30	M	19	NPH 85 R 15	195/105	H I	O 4+	80 131		neg	
R I	30 7	M	19 7	P 60 R 24	110/80	H I	T	32	82		neg
J I	21 6	F	19 8	P 18 R 30	122/80	O	O	31	65		neg

* O H A I B refer to negative hemorrhages aneurysms (micro) exudates and blind respectively

† O, T 1+ and 200 refer to degree of albuminuria zero trace one plus and 200 milligrams per cent

‡ Fulfill clinical criteria for K W syndrome

§ During pregnancy



FIG 23 2 KIMMELSTIEL-WILSON CHANGES (INTERCAPILLARY GLOMERULOSCLEROSIS) AT THE AUTOPSY OF A 25 YEAR OLD MALE WITH A 16 YEAR HISTORY OF DIABETES MELLITUS

Patient R A B had been maintained on 80 units of insulin (NPH 60 and regular 20) during the year preceding his death He was admitted with a 1½ year history of blurring vision and of leg edema of 6 months duration Blood pressure elevated to 180/110 bilateral retinal hemorrhages with new vessel formation profuse albuminuria azotemia up to 89 mg per cent diminished serum albumin (1.35 gm per cent) and elevated serum cholesterol levels (658 mg per cent) are in keeping with the clinical criteria for the K-W syndrome (Section kindly provided by Tom Moran M.D.)

low) have indicated that adrenocorticotropin or adrenocortical steroids may produce a remission in certain instances of the nephrotic syndrome

B Treatment of Nephrotic Syndrome with Adrenocorticotropin or Adrenocortical Steroids

Until recently therapy of the commonest forms of the nephrotic syndrome was only sporadically effective (13a–h) The type accompanying anticonvulsant drug therapy cleared spontaneously following withdrawal of the drug, the forms which appeared in childhood and were called either pure lipoid nephrosis a phase of glomerulonephritis, or a toxic reaction to sulfonamide resolved in a minority of cases during nonspecific supportive therapy or following endemic or induced exanthemata such as measles and chicken pox (22d) Adrenocorticotropin or cortisone when given in adequate pharmacologic dosage in the childhood form has altered the course considerably (22e–k) Thus in our series which now consists of 106

cases we have found that a remission can be induced in almost all instances during or following a 28-day course of adrenocorticotropin (100 mg per day), marked sodium restriction, a high intake of potassium supplemented by iron and vitamins, and prophylaxis with penicillin (22i) Thereafter recurrences appear in some 30 per cent of the children but respond to retreatment Intermittent therapy with cortisone following a successful remission seems to prevent recrudescence (22l, m), but the experience is as yet limited At any rate the outlook in the childhood type of nephrotic syndrome is somewhat brighter, though deaths do still occur when chronic nephritis and uremia supervene None of these children have had diabetes

In adults with the nephrotic syndrome the outlook remains grim for most patients irrespective of its etiology, since a regimen of 200 mg adrenocorticotropin with the supplementary features listed earlier induces a remission in only occasional patients, perhaps in one out of five In our small group of about 30 such patients three were diabetics with the Kimmelstiel-Wilson syndrome and none responded to therapy (22l)

Allen has described one case of uremia without retinopathy which improved on marked sodium and protein restriction (22n) Adrenalectomy or hypophysectomy have been reported to induce remissions of vascular disease in a minority of patients (22o–q) DDD which produces adrenocortical necrosis has also been used for this purpose (22r)

VI. The Less Frequent Ocular and Renal Disorders in Diabetes Mellitus

The dramatic upsurge of retinopathy and nephropathy in the past two decades, the more effective control of diabetes, and the availability of chemotherapeutic and antibiotic agents have distracted attention from some of the less frequent and the less lethal, but equally disabling, changes in the ocular and urinary system of the diabetic

A Eye Changes in the Juvenile Diabetic Other Than Retinopathy

A number of thorough reviews of the status of the lens iris, media, retina, and orbital musculature have been published (23a–e)

1. The Orbs. Clinical lore has long included recognition of the soft eyeballs in diabetic acidosis and coma believed to result from dehydration This is not, however, a specific sign and there are, of course, more direct indices of this complication

2. Extraocular Muscles. Paralysis of the eye muscles has occurred so infrequently in diabetes (18a 23a, 24a–c) that this may well represent a chance development, or be a part of a more general diabetic neuropathy

3. Corneae. Only rarely has wrinkling of the posterior surface been described (18a, 23a), perhaps because it is visible with a slit lamp only

4. Iris Iris changes are of two types rubeosis iridica diabetica, a very serious ocular complication characterized by new blood vessel formation on the anterior surface of the iris and recurrent hyphema, usually associated with an *intractable secondary glaucoma*, *diabetic iridopathy* with edema and vacuolization of the pigment layer of the iris and liberation of pigment into the aqueous humor (18a, 23a)

5. Pupillary Reactions The occurrence of *Argyll-Robertson pupils* in diabetes has been noted in Chapter 26 which deals with neuropathy

6 The Lens Refractive changes, *i e* a relative myopia with a blood sugar rise or relative hyperopia with its fall, are usually considered the result of fluid shifts (23f, 25a b) Corrective lens prescription is best deferred pending stabilization of these transient lens changes

In contrast, permanent alterations in the lens occur with cataract formation

a Cataracts occurring in the diabetic These are of two general types (23a, 26a–g) The first is indistinguishable from that observed in senescence in nondiabetics and in diabetics though it may occur more often in the latter group This type is only rarely seen in juvenile diabetes even after many years duration The other, variously known as the metabolic juvenile, or *diabetic cataract* (26c, o), *can develop very suddenly*, even in a matter of a few days (26b) It is characterized initially by subcapsular flocculation which results in a snowfall appearance and contrasts with the central striae of the senile type Care must be taken not to confuse these acquired changes with embryonic remnants such as the persistent hyaloid canal They cannot be differentiated, however, from the other metabolic cataracts such as those seen clinically in galactose intolerance in hypoparathyroidism, and after neutron irradiation nor from those produced experimentally by the extirpation of the pancreas by the maintenance of animals on diets deficient in tryptophan, or by feeding of monosaccharides such as galactose (27a–o)

b Etiology of metabolic cataracts occurring in diabetes The causes of cataract formation in the diabetic remain obscure It has been suggested that the *sulfhydryl group of glutathione in the lens* becomes reduced by hyperglycemia initiating irreversible lens changes (27g) It

nephropathy group in whom insufficient regulation has been etiologic factor (26g) They can occur, moreover, shortly after the *onset of* diabetes in children (26b) We have seen one such instance in a 12 year old girl (K V) two months after diagnosis and institution of adequate ther

apy and three months after the appearance of the first symptoms of diabetes (27p) This is unique in our experience though it has been reported by others In our series of almost 600 juvenile diabetics we have seen six other patients 12 to 15 years of age who developed obvious cataracts after one half to three years of diabetes These children were all considered to be well regulated by our criteria and had a lower than average incidence of acidosis or coma one episode per 16 years of diabetes in contrast to a general average of one per five years of diabetes in our group as a whole Recently Patterson has reported that provision of a high fat diet decreases the incidence of cataracts in diabetic rats He suggests that cataracts arise in hyperglycemic animals because glucose cannot enter the lens for energy purposes If a large intake of fat is provided however the energy needs of the lens are met and cataracts do not develop even though the same degree of hyperglycemia continues (27q r)

7 **Lipemia Retinalis** The striking refractile translucence in which the arteries and veins appear flat creamy or milky and tend to look alike used to be seen with greater frequency in the period prior to insulin and adequate regulation of diabetes Thus Parker and Culler (28a) found 36 published cases in 1930 and added two of their own In their patients the total blood lipids were 11 6 and 4 3 per cent respectively but it was pointed out that in the literature fat levels as high as 48 and 26 per cent were recorded They concluded that lipemia retinalis appeared only in acidosis with fat levels above 3 5 per cent Marble and Smith (28b) reviewed the 40 cases in the literature by 1936 and added nine cases of their own including two juveniles Lefkovits and Young (28c) reported a single case in 1950 in a young male diabetic who also had xanthomatous lesions of the skin The lipemia retinalis and most of the skin plaques disappeared promptly on regulation The paucity of cases since 1936 supports the conclusion that lipemia retinalis is a manifestation of poor control and the attendant hyperlipemia

8 **Optic Atrophy** This is mentioned as occurring in the series reported by Leopold (18a) and Waite and Beetham (23a)

9 **Weakness of Accommodation** This has been found in nearly 20 per cent of the diabetics (28d)

10 **Conjunctival Aneurysms** These occur about four times as commonly in the diabetic as in the nondiabetic

B Kidney Disorders Other Than Nephropathy

Urinary tract infections are probably the most frequent renal complication occurring in diabetes mellitus Barnard Story and Root for example reported urinary tract infections in 51 of 52 hospitalized adult diabetic females (29a) Autopsy series have shown a higher incidence of pyelo

nephritis in diabetic females than in similar age groups of nondiabetics of either sex or in diabetic males (29b) *The latter group, however, also has* an increased incidence It may be that in the female vulvitis in which glycosuria plays a part is a predisposing factor, in the males congenital lesions occur often enough to warrant a routine search for obstructions which serve as valves Bladder atony as a result of diabetic neuropathy will, of course, have a similar effect Pneumaturia may appear as a symptom (29c)

The therapy of urinary tract infections is difficult in general and more so in diabetics (29d) In view of the high incidence of urinary tract infections and of vascular disease in diabetics, it might well be profitable to obtain routine examinations *of the urinary tract of all diabetics at the time* the diagnosis is made This could take the form of intravenous or retrograde pyelography and would serve to identify those with congenital lesions, urinary tract obstructions, atony, etc, and permit prophylactic or remedial therapy

Other urinary tract disorders of rare occurrence but worthy of mention include renal papillary necrosis, cortical necrosis, and lower nephron nephrosis *The last of these* is discussed in *Chapter 18* as a complication of diabetic coma Renal papillary necrosis was first described by Friedreich (30a) and its higher association with diabetes was pointed out by Gunther (30b) This entity is characterized by the onset of fever, sepsis uremia, and coma in diabetics with urinary tract infection and obstruction Hematuria and colic may be present together with a roentgenographic picture not unlike that seen in renal tuberculosis It is more common in the older age group, especially after the age of 60 (30c–g) Experimental types have been produced by ligation of ureters and injection of pyogenic material (31a) and it has been noted in hydronephrotic ischemic *kidneys (31b)*

Summary

The older diabetic develops arteriosclerosis earlier and to a greater [illegible] sclerosis in

[illegible]

(aneurysmal dilatation of the retinal vessels, new vessel formation [illegible] of vision) and a nephropathy (albuminuria which may progress to nephrotic syndrome and renal failure) It is not certain at this time that the *degree of control* is causally related to the incidence of retinopathy and nephropathy Virtually no patient escapes retinopathy after 25 or more years of diabetes irrespective of its severity, and nephropathy in the form of the Kimmelstiel Wilson syndrome occurs most often in mild diabetics

It is possible, therefore that diabetics have an inherent predisposition to vascular disease (a higher incidence of hypertension is recorded amongst relatives of diabetics) In view of Keys findings in nondiabetics it could be too, that the fat content of the diet of diabetics further predisposes to angiopathy The other ophthalmologic and renal lesions in the diabetic occur less frequently and usually present less of a hazard to survival

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CHAPTER 24

The Gastrointestinal Tract and the Liver in Juvenile Diabetes

Disturbances of the gastrointestinal tract are far more crucial to the diabetic than to the nondiabetic Thus interference with food intake, nausea, anorexia, vomiting, abdominal pain, or diarrhea superimposes starvation upon the diabetes mellitus and thereby further diminishes the patient's ability to utilize carbohydrate If under such circumstances insulin is continued in the usual daily dosage, shock often results with further loss of carbohydrate tolerance, if insulin is omitted entirely ketosis and acidosis supervene with further losses of water and electrolytes via the urinary tract at a time when oral replacement is impossible The diabetic must, therefore, be trained to tread carefully between these two extremes, taking just enough insulin to avoid both ketosis and hypoglycemia until such time as oral intake is fully restored

The appearance of any of these gastrointestinal symptoms in a diabetic should immediately alert the patient, the family, and the physician to the possibility of imminent or present ketoacidosis If such complaints do not disappear in a matter of a few hours, the patient must be given maintenance or replacement therapy consisting of insulin, parenteral carbohydrate, water, and electrolytes Undue procrastination in the hope that the patient will improve spontaneously too often leads to frank acidosis or coma which has to be treated during the night and the early hours of the morning

I. Etiology of Nausea, Vomiting and Other Upper *Gastrointestinal Disturbances in the Diabetic*

It is inevitable that, irrespective of whether a rigid diet, moderate re

unlimited regimen is used in the

isis upon oral intake results It

ers" are relatively rare among

juvenile diabetics, since this does provide the child with a highly effective weapon in dealing with his family and society Actually in a series of detailed interviews with our juvenile diabetics and their families (1a) only 18 out of 215 patients were stated to have repeated or chronic difficulties

TABLE 24-1

Incidence of chronic or recurrent gastrointestinal complaints (based on interviews of 215 juvenile diabetics and their families)

None	Poor Eating Habits	Abdominal Pain	Nausea	Vomiting	Diarrhea	Constipation
172	18	11	7	6	4	10

with food intake or with gastrointestinal function (table 24-1). In this tabulation a history of transient and nonrepetitive anorexia, nausea, vomiting, abdominal pain or diarrhea was disregarded. We cannot decide from our data whether the diabetic child is more prone to such transient gastrointestinal disturbances than is the nondiabetic, because comparable control groups are lacking.

A. As a Manifestation of Ketosis or Acidosis

However, it is well recognized that nausea and vomiting frequently usher in the onset of ketoacidosis and coma (Ibid.) (see table 18-1 in Chapter 18). In a series of 188 such admissions in adults and children reviewed by the author and his colleagues (16) vomiting was present in about 75 per cent of the patients. A comparably high figure was obtained in our group of pediatric cases (15). It has been customary to view these gastrointestinal symptoms either as a manifestation of ketone body accumulation, dehydration, hyperglycemia and related biochemical changes or, if accompanied by fever or an endemic history, as evidence of an acute gastroenteritis of the infectious or food poisoning type.

B. Intrinsic Gastrointestinal Disease as a Possible Cause

Could these represent, however, a primary and intrinsic disturbance of the gastrointestinal tract rather than a secondary manifestation of ketosis or acute enteritis? To answer this question we have conducted routine radiologic studies of the gastrointestinal tract of diabetic children under adequate control. Such examinations in our own group of patients have yielded surprising results. In the course of 82 routine examinations of the upper gastrointestinal tract in diabetic children, Crozier, Danowski and Girdany (2) have found an ulcer crater in the duodenum of ten children and probable duodenal ulcers as indicated by marked deformities of the cap in two others. Examples are shown in figure 24-1. Antecedent symptoms referable to the gastrointestinal tract were not more pronounced nor more frequent in these children than in those who had negative examinations, nor was there a higher incidence of acidosis and coma. It could well be, therefore, that the nausea, vomiting and gastrointestinal distress in the diabetic does

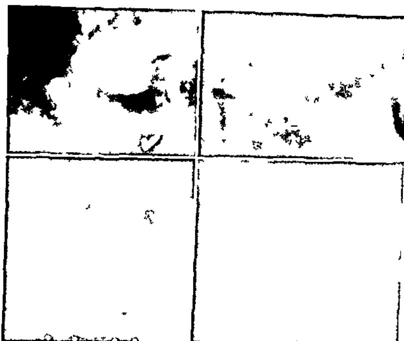


Fig. 24.1. Deformities of the Duodenum and Ulcer Craters in Juvenile Diabetic. Of 82 patients subjected to routine radiographic upper gastrointestinal examinations, duodenal deformities or ulcer craters were found in 12 (2a). Four examples are shown above.

at times result from such intrinsic lesions in the duodenum and does not represent a nonspecific manifestation of loss of diabetic regulation nor an acute gastroenteritis. Similar studies in a smaller number of adult diabetics have shown essentially the same results (2b). Though it may be argued, and with reason, that these radiologic findings merely represent a variation of normal, acceptance of this as an explanation would necessitate revision of our views of a "negative gastrointestinal series." The possibility that these abnormal findings in our studies were attributable to lactose dissolved in the barium suspension to prevent hypoglycemia have been excluded by use of an intravenous infusion of glucose for this purpose. Actually, increasing evidence is appearing that peptic ulcers are more common in infants and children than has been hitherto believed (2c–g).

Chapman and Loeb (2h) point out that though considerable study has been directed to the role of emotions in peptic ulcer in adults, very little has been reported regarding such factors in children. They cite data of their own and of other workers (2i, j) which indicate that children who develop peptic ulcers are subnormally assertive and have much discomfort and

anxiety regarding the expression of aggressive (anger) or self-assertive feelings. The presumption is that they react to emotional stress with upper gastrointestinal dysfunction, i.e., hypermotility, hyperemia, and hyperacidity. We have at present insufficient data to determine whether the diabetic child who develops a duodenal ulcer has comparable emotional and personality patterns. Similarly our observations on free hydrochloric acid and pepsinogen secretion which in increased amounts help identify ulcer susceptible individuals (2k, l) are limited. Rabinowitch's report (2m, n) of achlorhydria in 39 per cent of his diabetics was based on studies in adults.

II. The Small and Large Intestine of the Diabetic

A. Roentgenographic Studies

It has been recognized that in diabetics roentgenograms of the jejunum and ileum at times revealed aggregates of barium referred to as "puddling" or as the "moulage" sign (3). Since these were also seen in patients with nutritional disturbances such as sprue and celiac disease and were thought to result from a vitamin lack, they have been termed "deficiency patterns."

Daytime and nocturnal diarrhea has also been a troublesome symptom in a small number of patients with diabetes (4a, c). In five of the series of 40 such patients reported by Sheridan and Bailey (4c) the diabetes began during childhood between the ages of six and 16 and the diarrhea appeared eight to 18 years later. This disturbance in gastrointestinal function is believed to represent neuropathy involving the autonomic system (4b, d) (see Chapter 26) and is to be differentiated from steatorrhea occurring in a diabetic as a result of pancreatic insufficiency or other disturbance in fat absorption (4e, f).

Radiographic examinations have been made at random in 82 of our diabetic children (2a, b) with the finding that abnormalities in the distribution pattern of barium in the small bowel may be present without clinical symptoms. This was true in seven of the 82 examinations. Two of these are illustrated in figure 24-2. The origin and significance of these changes are unknown. The examinations of the large bowel in these same 82 children 24 hours after oral barium as well as after barium enema showed no abnormalities.

B. Fecal Excretion of Electrolytes and of Nitrogen in Diabetic Children

In table 24-II the fecal excretion of sodium, potassium, chloride, and nitrogen in a group of diabetic children has been compared with the findings in nondiabetic pediatric patients. Feces were collected during intervals of three to nine days with the beginning and end of study periods marked by carmine red administration (4g, h). The average values for these fecal

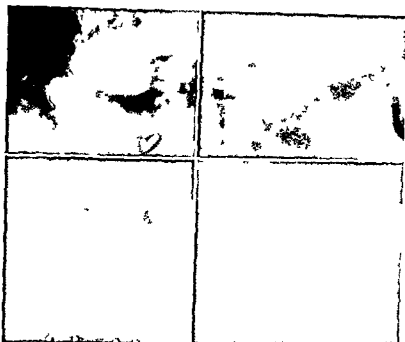


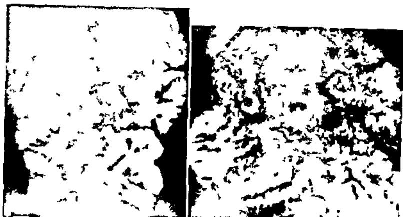
FIG 24 1 DEFORMITIES OF THE DUODENUM AND ULCER CRATERS IN JUVENILE DIABETICS Of 82 patients subjected to routine roentgenographic upper gastrointestinal examinations duodenal deformities or ulcer craters were found in 12 (21 1) Four examples are shown above

at times result from such intrinsic lesions in the duodenum and does not represent a nonspecific manifestation of loss of diabetic regulation nor an acute gastroenteritis Similar studies in a smaller number of adult diabetics have shown essentially the same results (2b) Though it may be argued and with reason that these radiologic findings merely represent a variation of normal acceptance of this as an explanation would necessitate revision of our views of a negative gastrointestinal series The possibility that these abnormal findings in our studies were attributable to lactose dissolved in the barium suspension to prevent hypoglycemia have been excluded by use of an intravenous infusion of glucose for this purpose Actually increasing evidence is appearing that peptic ulcers are more common in infants and children than has been hitherto believed (2c–g)

Chapman and Loeb (2h) point out that though considerable study has been directed to the role of emotions in peptic ulcer in adults very little has been reported regarding such factors in children They cite data of their own and of other workers (2i, j) which indicate that children who develop peptic ulcers are subnormally assertive and have much discomfort and

TABLE 24 II
Fecal electrolytes and nitrogen in diabetic and nondiabetic children

Pt	Age	Sex	Diagnosis	Diet	Feces: Interval	Feces: Wgt	Feces: Cl	Feces: Na	Feces: K	Feces: N
					days	gm	mEq	mEq	mEq	gm
W W	12	M	Diab mell	Milk formula	6	643	7	7	102	5 8
C A S	9	F	Diab mell	Milk formula	6	55	1	3	9	0 8
J Mc	15	M	Diab mell	Diabetic diet	6	708	5	57	53	10 0
K Mc	11	F	Diab mell	Diabetic diet	6	494	5	11	44	7 9
F B	14	M	Diab mell	Milk formula	7	816	11	19	103	6 6
J V	15	M	Diab mell	Milk formula	7	774	5	27	103	9 6
M J	12	M	Diab mell	Milk formula	5	252	3	7	78	4 1
M B	11	F	Diab mell	Milk formula	5	330	3	11	61	7 1
K R	15	M	Diab mell	Milk formula	5	405	6	5	139	6 9
J C	15	F	Diab mell	Diabetic diet	4	111	1	3	16	1 6
B S	12	F	Diab mell	Diabetic diet	4	212	0	4	27	4 2
J J	7	F	Diab mell	Low Na milk formula	5	187	10	21	2	5 7
L T	9	M	Diab mell	Low Na milk formula	5	337	4	6	44	3 9
H D	16	F	Diab mell	Low Na milk formula	5	409	2	5	65	7 0
W S	9	M	Diab mell	Low Na milk formula	5	512	6	16	73	7 0
D Y	12	M	Nephrosis	Low Na milk formula	6	1171	11	26	48	6 3
W G	12	M	Nephritis	Low Na milk formula	5	470	5	6	96	5 2
					5	299	3	9	51	3 7
				"	5	534	6	3	90	5 9
					5	475	5	6	77	6 8
				"	5	752	5	31	288	7 2
W G	12	M	Nephritis	Low Na milk formula	5	782	5	31	288	7 2
B F	6	M	Nephrosis	Low Na milk formula	6	607	—	17	52	4 2
					6	685	13	5	71	5 2
K M	3 5	F	Nephrosis	Low Na milk formula	6	905	13	12	47	7 9
				"	3	196	1	5	28	1 6
D W	6	M	Nephrosis	Full diet	7	80	3	3	21	0 9
D Y	12	M	Nephrosis	Low Na milk formula	7	837	11	10	41	6 1
				"	6	864	6	4	99	8 8
				"	9	1019	1	9	65	9 0
				"	6	1063	17	78	52	10 9
				"	4	677	1	23	13	3 4
R D	13	M	Obesity	Unrestricted	4	519	2	6	50	5 6



FIGS 24 2A AND 2B SMALL BOWEL DEFICIENCY PATTERN IN TWO JUVENILE DIABETICS In these 2 children the roentgenological abnormality was unassociated with any symptoms or complaints In 82 such routine examinations in juvenile diabetics 5 other patients with similar changes were found for a total of 7 (2a b)

constituents are of the same order of magnitude for the two groups thus chloride excretion in diabetics and nondiabetics was 0 8 and 1 2 mEq per day respectively sodium 2 4 and 2 9 mEq per day, potassium 11 5 and 15 6 mEq per day, and nitrogen 1 1 and 1 0 gm per day

III The Liver in the Diabetic: Basic Physiology and Biochemistry

In the diabetic as in the nondiabetic the liver is an important factor in *the storage manufacture and release of the glucose fatty acids and* amino acids from which the organism derives energy, and acetyl CoA for tissue growth and replacement and for activity

1 *Role of the Liver in the Storage and Release of Carbohydrate*

Monosaccharides present in diet or produced during hydrolysis in the gastrointestinal tract reach the liver via the portal circulation Some of the individual sugars are then polymerized into glycogen after transformation into glucose 1-phosphate (5a) (see Chapter 1) The rate at which this occurs is probably influenced by factors such as the morphologic integrity of the liver (5b–d) the amount of hepatic glycogen (5e f) the chemical structure of the monosaccharide (5g h) the rate of glucose formation from amino acids (5i) the lactic acid load from muscular activity (5j), and the availability of insulin (5c f k) Though insulin accelerates glycogen formation in the presence of adequate carbohydrate loads glycogenation can and does occur in the absence of this hormone (5l) During intervals

phosphorus 2 83 gm total cholesterol, and 79 5 mEq neutral fat per kg of wet tissue This is drawn either from dietary sources, even though absorption of fats via the lacteals into the thoracic duct chyle largely by passes the hepatic circulation (7b) or from the conversion of acetyl CoA (7c) Isotope studies indicate that there is a constant flux of the liver fat and the total amount changes only when the net flux is other than zero (7d) Paucity or absence of certain lipotropic substances such as choline betaine or inositol interferes with this dynamic equilibrium and fatty livers result (8) In alloxan diabetic animals the utilization of glucose for lipogenesis and the oxidation of fat are both greatly decreased (9a b) Provision of insulin so greatly augments the first of these processes that a several fold increase in liver fat occurs during the first three or four days During this same period oxidation of fats by the liver remains reduced and therefore at least two factors overproduction and underutilization contribute to this increase in fat Similarly complex relationships are presumably operative in clinical diabetes

The work of Mirsky and his colleagues has established that the liver is the chief site of ketone body production (10a–c) Deglycogenation of the liver occurring in the course of starvation or in diabetic ketosis and acidosis accelerates the formation of these four-carbon compounds from acetyl CoA produced by the successive beta oxidation of mobilized fat In alloxan diabetic rats however both fed and fasted hyperketonemia can appear without depletion of liver glycogen (10d) In any case the limited ability of the tissues to utilize them estimated at 2 5 gm of fat per kg per 24 hours in the nondiabetic (10e) is surpassed and ketonemia and ketonuria appear

IV. The Size and Function of the Liver in Diabetes Mellitus

A Hepatomegaly in Uncontrolled Diabetes

During the second decade of insulin therapy of juvenile and adult diabetics a number of workers concurred that the liver was enlarged with surprising frequency in diabetes mellitus and especially in juvenile diabetics (11a–c) that in some children this was accompanied by stunting of body growth (11d e) and that the hepatomegaly occurred most often in diabetic acidosis and coma particularly during the recovery phase (11a) No systematic studies of liver function tests in these patients were reported but it was noted that the occasional measurements of the bilirubin level bromsulfalein excretion cholesterol ratio (11b) and urine urobilinogen output (11a) were within normal limits Hanssen reported that the icterus index was elevated in the few patients in whom this was measured (11a) Isolated analyses of liver specimens obtained at autopsy revealed increased glycogen and fat concentrations (11b)

between the ingestion of food the liver provides a steady supply of glucose to the extracellular fluid and to the tissue cells by releasing stored glycogen (5m), and as indicated in section B, by gluconeogenesis

In the diabetic patient both glycogen formation and release of stored glycogen play a more important role in glucose homeostasis than in non diabetics In the latter the output or action of insulin is governed by the carbohydrate load and is increased or reduced as needed In the diabetic *insulin action* continues unabated even when intake is zero and has to be counteracted by release of glycogen and by gluconeogenesis

B The Liver and the New Formation of Carbohydrate

The stores of liver glycogen even in a well nourished child or adult or a well controlled diabetic are quite limited amounting to 100 to 150 gm of glucose (5n) It is obvious, therefore, that this is but an emergency ration sufficient for approximately one day and must be supplemented by glucose from other sources This need is met by gluconeogenesis from protein and from glycerol and possibly from fatty acids (5i, 6a b) This new formation of sugar also occurs in the kidney (6c) and perhaps in other organs as well The relative magnitudes of the hepatic and extrahepatic components of gluconeogenesis are readily illustrated by hepatectomy In such preparations the contribution of gluconeogenesis from tissues other than the liver is inadequate to prevent marked hypoglycemia nor is the utilization of amino acids for this purpose by such tissues sufficient to prevent a rise in plasma amino acid (6d e) The process of gluconeogenesis occurs at a low rate when liver glycogen is high and available and much more rapidly when the stores are being withdrawn or become depleted (6f, g)

The particular amino acids which are capable of conversion to glucose or glycogen have been listed in Chapter 1 together with an indication of the order in which the proteins are summoned from the body tissues Cathe terizat [illegible] ment on of the magni [illegible] liver a [illegible] mg of glucose per kilogram per minute at a urea glucose ratio of [illegible] (6f h) In the diabetic in ketosis and acidosis in whom liver glycogen is depleted this contribution rises significantly, returning to usual fasting values as the diabetes is again regulated The antianabolic effect of the adrenocortical 11 oxysteroids and the role of excesses of thyroid hormone in accelerating such gluconeogenesis have been presented in Chapters 3 and 4

C Fat Metabolism in the Liver

The total fat content of 'normal' human liver as reported by Ralli *et al* (7a) includes an average of 128 mEq of fatty acids, 0 8 gm lipid

phosphorus, 2 83 gm total cholesterol, and 79 5 mEq neutral fat per kg of wet tissue This is drawn either from dietary sources, even though absorption of fats via the lacteals into the thoracic duct chyle largely bypasses the hepatic circulation (7b), or from the conversion of acetyl CoA (7c) Isotope studies indicate that there is a constant flux of the liver fat, and the total amount changes only when the net flux is other than zero (7d) Paucity or absence of certain lipotropic substances such as choline, betaine, or inositol interferes with this dynamic equilibrium and fatty livers result (8) In alloxan diabetic animals the utilization of glucose for lipogenesis and the oxidation of fat are both greatly decreased (9a, b) Provision of insulin so greatly augments the first of these processes that a several-fold increase in liver fat occurs during the first three or four days During this same period oxidation of fats by the liver remains reduced and therefore at least two factors, overproduction and underutilization, contribute to this increase in fat Similarly complex relationships are presumably operative in clinical diabetes

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The particular amino acids which are capable of conversion to glucose or glycogen have been listed in Chapter 1 together with an indication of the order in which the proteins are summoned from the body tissues Catheterization of the hepatic artery and vein has permitted estimation of the magnitude of these contributions Thus in the fasting normal subject the liver and the organs drained by the splanchnic system provide 3 4 ± 0 5 mg of glucose per kilogram per minute at a urea glucose ratio of 0 06 (6f h) In the diabetic in ketosis and acidosis in whom liver glycogen is depleted this contribution rises significantly, returning to usual fasting values as the diabetes is again *regulated* *The antianabolic effect* of the adrenocortical 11 oxysteroids and the role of excesses of thyroid hormone in accelerating such gluconeogenesis have been presented in Chapters 3 and 4

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TABLE 24 III

Liver function studies in juvenile diabetics

Patient	Age	Body Wt.	Duration of Diab	Insulin Rx	Thymol Turbidity	Ceph Floc		Serum Alk P'ase	Serum Total Bilirubin	BSP Retention	Serum Total Cholesterol	Prothrombin Time		Serum Alb -Glob	
						24 hr	48 hr					Pt.	Control	Alb	Glob
		kgm			McL u			Bod u	mg %	% 0 45	mg %	sec	sec	gm %	gm %
J S	15 yr 5 mo	51	2 yr	L 34	0	0	1+	12 9	<0 5	0	246	12	12	4 82	3 02
J S	14 yr 2 mo	42	4 yr	L 40	0	0	1+	8 9	<0 5	0	206	12	12	4 53	3 02
F M	11 yr 2 mo	42	6 yr	L 60	0	1+	1+	13 2	<0 5	0	131	20	12	4 43	3 27
S H	11 yr 11 mo	37	7 yr	L 24	1 5	+-	0	13 7	<0 5	0	314	12	12	3 96	2 55
W D	16 yr	64 8	9 yr 5 mo	NPH 50 Reg 10	1 5	1+	1+	5 8	<0 5	0	238	15	12	4 62	3 32
J K	13 yr 6 mo	42	7 yr 5 mo	L 35	0 5	+-	-0	5 1	<0 5	0	274	12	12	2 94	4 56
E M	14 yr 4 mo	32 6	11 yr 5 mo	PZI 10 RLG 20	0 5	+	0	10 7	<0 5	0	188	15	15	4 76	2 83
J W	11 yr 2 mo	37 2	2 yr 4 mo	L 22	1 5	+-	1+	13 6	<0 5	2	266	—	—	4 60	3 00
G M	15 yr 1 mo	52 6	3 yr 1 mo	L 40	1 0	+-	0	11 2	<0 5	0	154	13	15	3 09	2 59
E M	14 yr 1 mo	40 6	1 yr 1 mo	REG 20 NPH 18	1 0	1+	1+	NSQ	<0 5	0	207	13	14	4 86	2 61
W G	13 yr 2 mo	46 8	1 yr 1 mo	REG 11 L 20	1 0	1+	+-	5 9	<0 5	4	216	14	13	—	—
W B	13 yr 7 mo	53	2 yr 2 mo	L 62	0 5	+-	+-	13 4	<0 5	4	250	12	13	4 48	2 90
M C	15 yr 4 mo	35	12 yr 3 mo	L 40	0 5	0	0	10 6	<0 5	0	266	13	13	3 79	3 72
B S	10 yr 5 mo	38 6	8 yr	L 52	1 0	+-	+-	21 11 3	<0 5	<2	—	16	15	4 41	3 12
J S	8 yr 4 mo	25	2 yr 1 mo	PZI 18 RLG 42	2 0	+-	+-	10 6	<0 5	0	—	14	13	4 17	2 38
W S	12 yr 11 mo	38	3 yr 8 mo	PZI 13 RLG 28	3 0	1+	1+	23 2	<0 5	2	—	13	12	4;14	4 21
G B	10 yr 1 mo	36	1 yr 1 mo	L 16 REG 3	1 5	+-	1+	12 6	<0 5	0	216	12	12	4 24	2 90
H P	10 yr 3 mo	32 4	5 yr 9 mo	L 2 REG 15	1 0	1+	1+	15 6	0 6	2	229	12	12	4 61	2 95
D D	7 yr 10 mo	25 6	7 yr	L 20 RLG 7	1 0	+-	1+	15 7	<0 5	2	233	13	12	4 17	3 59
L S	11 yr 11 mo	42	2 yr	L 30	1 5	1+	1+	12 8	<0 5	—	180	—	—	4 56	2 47
L Y	11 yr 7 mo	58	0 yr 7 mo	L 40	1 5	1+	1+	2 8	<0 5	—	—	—	—	—	—
S L	13 yr 1 mo	39 2	4 yr	PZI 8 REG 28	1 0	+-	+-	17 3	<0 5	—	183	—	—	5 43	3 49

Hanssen also demonstrated that hospitalization with improvement of diabetic regulation regularly decreased the size of the enlarged liver (11a), other workers indicated that the advent of protamine zinc insulin also reduced the incidence of hepatomegaly (11c, d) This was ascribed to more adequate control of carbohydrate metabolism, though in at least one report the opinion was voiced that this was to be attributed to a higher intake of protein (11f) Hepatomegaly continues however, to be a moderately frequent finding in diabetes despite the use of long acting insulins and more generous diets (11f–i) In our experience hepatomegaly in diabetic children occurs most often during recovery from acidosis or coma We have no data on the contributions of water retention and of glycogen and fat deposition to this enlargement

B Abnormalities of Liver Function Indices

Prior and subsequent to these comments on hepatic enlargement there have appeared sporadic reports of liver function indices without reference to the size of the organ (12a–j) Thus Rabinowitch (12b c) reported hyperbilirubinemia in 30 of 130 patients, and Gray, Hook, and Batty (12d) indicated that the serum colloidal gold reaction, believed by them to be a sensitive measure of liver function (12e), was positive in 91 of 247 patients Leevy *et al* (12f) state that 149 of 380 diabetics had abnormalities of one or more of the following bromsulfalein excretion cephalin flocculation serum cholesterol, albumin, globulin, or bilirubin concentrations Twenty four of their patients were under 20 years of age and seven showed hepatic dysfunction by their criteria Needle biopsies of the liver were obtained in 30 of their patients, including four of the young diabetics Of these one had normal function and a negative liver biopsy The other three had abnormalities of function with fat infiltration in two of the three Other workers have reported, however, that liver function is quite normal in diabetes even following recent acidosis, when indices such as thymol turbidity, cephalin flocculation, albumin globulin bilirubin prothrombin concentrations, and icterus index were used (12g) In this series five of the patients fell into the juvenile diabetes category with the duration prior to the liver tests varying from one and one half to 15 years The reports by Zimmerman *et al* (12h, i), Frankel, Asbury, and Baker (12j), and others (12k) are in keeping with the above

It would appear therefore, that in most diabetic patients hepatic function is not grossly impaired when evaluated by the ordinary techniques and that in those instances where abnormal results were obtained a clear relationship to hepatic disease has not been established This is in line with the experience in a group of our diabetic children in whom virtually no abnormalities of cephalin flocculation thymol turbidity, bromsulfalein

unduly susceptible to intrinsic disturbances of the gastrointestinal tract which can themselves initiate anorexia nausea and vomiting

The key role of the liver in the intermediary metabolism of foodstuffs and insulin resistance have been cited as the explanation for difficulties in regulating diabetes in patients with hemochromatosis Though poorly controlled diabetes is frequently accompanied by hepatomegaly, there is no evidence that indices of hepatic function are consistently disturbed in these or in well regulated diabetics It may be however that abnormal indices are encountered more often in diabetics than in nondiabetics

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excretion, serum alkaline phosphatase, serum albumin, globulin, and free and total bilirubin were encountered (table 24-III) It may well be that the occasional abnormalities seen in diabetes mellitus are no more frequent than the unexpected deviations from normal encountered by Neefe *et al* (*12l*) in the nondiabetic controls assembled by them for comparison with infectious hepatitis patients

V. Hemochromatosis

In adults the coincidence of carbohydrate impairment, cirrhosis, and a bronzing of the skin is termed hemochromatosis or bronze diabetes (13a-d) In this entity the diabetes is at times difficult to control This undoubtedly reflects compromise of the glycogen storage release and gluconeogenic functions of the liver in glucose homeostasis It may be related however to insulin resistance (13e, f) (see also Chapter 20) These instances are rare among adult diabetics and have not been reported in children

VI. Carbohydrate Disposal in Cirrhosis with Hepatic Insufficiency

It has been recognized that glucose tolerance tests (14a, b) and other indices of carbohydrate metabolism are abnormal in cirrhosis which is sufficiently advanced to produce persistent abnormalities in bromsulfalein excretion, in serum bilirubin, prothrombin, cholesterol and cholesterol ester levels, and in other tests These take the form of an unusually high early peaking of blood sugar levels after oral or intravenous glucose with a return toward but not entirely to normal at two hours (14c) The undue hyperglycemia presumably reflects the well-recognized inability of a liver involved by a disease process to lay down glycogen

Studies of the serum inorganic phosphorus levels in such patients show, however, a greater than usual decline which can be taken to indicate an accelerated rate of glycolysis From these observations it appears that in the cirrhotic the tissues play a greater than normal role in disposing of the greater glucose load resulting from the inability of the liver to lay down glycogen

Summary

The frequent antecedents of anorexia, nausea, and vomiting of ketosis, acidosis, and coma have been attributed to the dehydration and the other accompanying biochemical disturbances Routine survey of the gastrointestinal tract of juvenile diabetics in our clinic has revealed an unexpectedly high incidence of duodenal deformities, ulcer craters, and small bowel deficiency patterns This suggests that the juvenile diabetic may be

unduly susceptible to intrinsic disturbances of the gastrointestinal tract which can themselves initiate anorexia nausea and vomiting

The key role of the liver in the intermediary metabolism of foodstuffs and insulin resistance have been cited as the explanation for difficulties in regulating diabetes in patients with hemochromatosis Though poorly controlled diabetes is frequently accompanied by hepatomegaly there is no evidence that indices of hepatic function are consistently disturbed in these or in well regulated diabetics It may be however that abnormal indices are encountered more often in diabetics than in nondiabetics

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CHAPTER 25

Fertility and Outcome of Pregnancy in Juvenile and Adult Diabetes

Prior to the availability of insulin the juvenile diabetic rarely lived long enough to reach the childbearing age Furthermore, only the patients with the mildest forms of adult diabetes succeeded in carrying a pregnancy to term and giving birth to a normal infant who survived This bleak outlook has altered considerably, but the diabetic patient of the juvenile or adult type who becomes pregnant still undergoes many risks The greater maternal mortality rate has fortunately been largely eliminated, lowered fertility, if present, and the greater losses of pregnancies through abortions, premature deaths, stillbirths, congenital anomalies, and neonatal deaths recorded in the pre-insulin days remain as problems which must be viewed as complications or concomitants of diabetes

I. The Maternal Risk

A Mortality and Incidence of Toxemia and Hydramnios

Pregnancy used to present a greater hazard to the diabetic than to the nondiabetic mother Maternal death rates ran as high as 55 per cent in diabetic pregnancies (1a–g), but it must be remembered that 40 to 60 per cent of the diabetic deaths in the pre insulin era were attributable to the disease itself In more recent years the reported rates have fallen down to or below those in the population as a whole (1h–n, 2a–p) Bachman's summary (1n) of 599 pregnancies in British clinics and 850 in American clinics revealed a maternal mortality of 20 and of seven per 1000 for the two groups, respectively The individual reports which make up his pooled data and isolated earlier and later reports by other workers are summarized in table 25-I From the same table it is evident that the incidence of pre-eclamptic toxemia, hypertension, and hydramnios has been and continues to be formidable In Bachman's compilation (1n) the patients in American clinics showed a 25 1, 7 3, and 15 6 per cent incidence for pre eclamptic toxemia, hydramnios, and vascular hypertension, respectively In the British experience the figures for the first two were 17 0 and 27 7 per cent with no data on vascular hypertension It is our impression in Pittsburgh (2j, k) that the toxemia rate in diabetics continues to be higher than in

TABLE 25 I

Pregnancy in diabetes mellitus maternal and fetal neonatal mortality with some note of the incidence of toxemia and hydramnios

Authors	Ref	Period of Study	Number of Cases	Toxemia	Hydramnios	Maternal Mortality	Fetal Mortality*
				%	%	%	%
Vinay	1a	1894	34			55	48
Ruoff	1b	1903	66			46	53
Stengel	1c	1904	19			26	50
Chapiet	1d	1907	103			25	27
Williams	1e	1909	66			27	41
Wilder and Parsons	1f	1928	55			12	47
Skipper	1g	1933	118			9	45
Hurwitz and Irving	1h	1916–1937	51			2	25–12
Lavietes Leary, Winkler, and Peters	1i	1921–1943	31	32	16	0	39
Bill and Posey	1j	1933–1944	44	27	2 3	4	27
Joslin	1k	1931–1945	210	33		0 5	16
Pedersen	5m,n	1926–1945	156	30	20		38
Randall	1l	1933–1946	50	18			20
Rike and Fawcett	2j	1937–1946	55	33		4	29
Palmer, Crampton, and Barnes	5c	1944–1947	39				40
Patterson and Burnstein	2a	1937–1947	71	41	8	7	35
Barns and Morgans	2b	1929–1948	58	43	20	2	47
Given, Douglas, and Tolstoi	2d	1930–1948	131	46		2	21–30
Zilliacus	2c	1934–1948	32	41	9	0	72
White	5a	1934–1948	439	50		0 2	18†
Hall and Tillman	5k	1923–1949	147	32	9 6	0 7	21
Oakley (British Hosp)	2f	1942–1949	458	19		3	43
Moss and Mulholland	4b	1929–1949	42	43	9 5	0	55
Reis, DeCosta, and Allweiss	2l	1935–1949	59	10 2	9 5	0	14
Snyder	1m	1939–1950	131	28		0	12
Hurwitz and Higano	2g	1932–1950	140	29			23
Whiteley, Adams, and Parrott	5b	1941–1952	72	24	21	0	19 4
Pedersen	5m n	1945–1952	149	30	50		27
Tolstoi, Given, and Douglas	2e	1950–1953	72	36	33		32‡
Oakley (King's College)	2f	1942–1953	275	11		1 5	27
Bergqvist	3k	1938–1953	43			0	44
Dolger, Bookman, and Joelson	5o	1953–1955	100				20

* Fetal, stillbirth, and neonatal deaths

† 11 per cent in a sub series

‡ Includes cases reported in literature

nondiabetics, though the statistics of Reis, DeCosta, and Allweiss (2l, m) show an incidence of 10 2 per cent, a rate almost as low as the eight per cent observed in nondiabetics (2n) These authors suggest that their low incidence is explained in part at least by careful exclusion of nephropathy and hypertension which antedate the pregnancy and are properly attributable to the diabetes itself It may be, however, that the frequency has been reduced *pari passu* with the decrease in the population as a whole by measures such as control of body weight gain, therapy of urinary infections, and sodium restriction (2q)

B Effect of Pregnancy upon Carbohydrate Metabolism and the Course of Maternal Diabetes

Particular care must be taken throughout pregnancy but especially following delivery to avoid confusion of glucosuria and galactosuria (3a–c) The latter when present will of course result in overinsulinization The differentiation of these two forms of glycosuria even with careful yeasting of urine specimens or using newly developed enzymatic determination of *urine glucose may be difficult (2m) and is discussed in Chapters 8 and 13*

1. Renal Threshold and Glucose Tolerance Changes in Nondiabetic and Diabetic Pregnancies. Earlier studies of carbohydrate metabolism during nondiabetic pregnancies have indicated that gestation quite regularly lowers the "renal threshold" for glucose and decreases carbohydrate tolerance in some patients (3d–g) Johnson and Bonsnes (3h) using an intravenous and Cobley and Lancaster (3i) employing an oral glucose tolerance test were unable to confirm the latter finding However, there is new evidence that the renal tubular mass involved in the reabsorption of filtered glu[illegible] first trimester of pregnancy [illegible] nce is normal in pregnancy [illegible] nic phosphorus is less than usual (3l) Lund and Weese (3m) suggest that if the mother gives birth to a large baby the incidence of abnormally elevated glucose tolerance curves during pregnancy rises from the usual value of eight per cent to 50 per cent

2. Insulin Requirements During and Following Diabetic Pregnancies. Impressions and reports of the effect of gestation upon the clinical course of pre existent diabetes vary Thus Patterson and Burnstein (2a) state that the insulin requirement was usually unaffected, occasionally fell, and more frequently rose *In the report by Barns and Morgans* (2b) carbohydrate tolerance is described as decreasing in the majority as pregnancy progressed, *but increasing in some.* In Zilliacus' series (2c) an equal percentage showed no change or an increase in severity, while a decrease occurred in only two Given *et al* (2d, e) indicate that in 131 preg-

nancies there was no improvement as reflected in insulin needs on Tolstoi's liberal regimen and ketoacidosis appeared in 16 8 per cent Oakley (2f) states that the insulin requirement rose during the second and third trimester in 75 per cent of the patients Duncan's and Fetter's early report (3n) describes a rise in insulin requirement in the first and third trimester and hypoglycemia after delivery Pedersen (3o) and Bergqvist (3p) in more recent series concur in finding an improvement in the first few months and an aggravation in the severity of the diabetes in the final months of pregnancy In Jones' series only rarely did the requirement decrease with an increase recorded in more than half (3q)

These published experiences can be summarized by saying that in a minority of the patients the course of the diabetes appears to be uninfluenced, in the majority the severity of the diabetes and the problems of regulation increase, in only a few patients is the intensity of the diabetes decreased and its control simplified In terms of insulin needs some have stated that the requirement falls and others that it rises during the first trimester whereas there is more uniform agreement that the dosage definitely increases during the third trimester and that ketoacidosis is particularly frequent Following delivery an increase in carbohydrate tolerance usually becomes manifest and hypoglycemia may appear if insulin administration is not correspondingly reduced In terms of eventual effects White has noted that the ultimate insulin requirement tends to decline following two or more pregnancies (3r)

II. The Fetal Risk

It has been repeatedly stated that in pregnancy diabetes presents much more of a hazard to the fetus than to the mother

A Fertility and Fetal Wastage in the Diabetic

Though some workers maintain that the incidence of sterile marriages is no greater in diabetics (2m 4a, b), fertility as measured by successful initiation and completion of pregnancy is certainly decreased Thus, in the Zilliacus series (2c) there were 32 diabetic patients in 31 976 consecutive deliveries This ratio of one diabetic to every 1000 nondiabetic mothers is considerably less than the estimates of the probable incidence of diabetes in women in the childbearing age as a whole based on the Oxford Survey (4c), seven per 1000 for the group between 15 and 44 years of age However, calculations limited to term pregnancies provide no information as to what proportions of the decrease in fertility, in the sense stated above, are to be ascribed to a diminished rate of conception and to very early losses of imbedded ova and embryos The higher rate of recorded abortions and premature deaths known to be present in diabetics (table

TABLE 25 II

Probable fertility and the incidence of abortions, stillbirths, and neonatal deaths in nondiabetics, prediabetics, and diabetics

Authors	Ref	Nondiabetics				Prediabetics				Diabetics			
		Sterility	Abortions	Still Births	Neonatal Deaths	Abortions	Still Births	Neonatal Deaths	Total Fetal Death Rate*	Fertility	Abortions	Still-Births	Neonatal Deaths
		%	%	%	%	%	%	%	%	%	%	%	%
Skipper	1g								39.3	15†			
Paton	8a									7.3‡			
Hamblen	4a	10											
Herrick and Tillman	5d												
Eastman	5e		10							Decr	16–25	25	18
Moss and Mulholland	4b					12.2	8.5	6.7	27.4	Norm	21.4	26.2	7.1
Barns and Morgans	8b		11.8			13.3			20.5		14		
Mengert and Laughlin	5f					17.9	11.9		29.8		26.2	17.8	
Stander	5g			2.14	1.21								
Engelhardt and Melvin	5h											21.5	
Bill and Posey	1j												11.4
Dolger and Herzstein	8c								23.8				
Miller	7c								19.8				
Patterson and Burnstein	2a								23	Norm			
Palmer, Crampton, and Barnes	5c								27				
White Titus, Joslin and Hunt	5i								20				
Reis DeCosta and Allweiss	21					18.8	3.5	3.5					

* Sum of abortions, stillbirths, and neonatal deaths
† % of pregnancies in Skipper's series in years 1893–1922
‡ Sterility in diabetics

25 II) suggests that the latter is undoubtedly an important and possibly even the sole determinant of the reduced fertility The reports of the over-all fetal loss range from more that 70 per cent down to 11 per cent and are summarized in tables 25-I and 25 II (5a–p) It should be kept in mind, however, that these statistics are not comparable because of the variety of methods employed in presenting the outcome of such pregnancies

1 Role of Ketoacidosis and Coma or Insulin Shock. Some of the abortions, premature deaths, and stillbirths are known to occur following diabetic ketoacidosis and coma or insulin hypoglycemia (2a, e, 5a), but these are not necessary precursors (2m) Understandably, younger diabetics do better (2a) The most extensive reports on the complications and outcome of pregnancy in diabetes are those of the Joslin group (1k, 5a i) These include 439 viable births of which 58 per cent occurred in former juvenile diabetics In one segment of this series treated with estrogens in accordance with the recommendations of Smith and Smith (5a, 6a), the fetal mortality was the lowest ever reported, 11 per cent It is of interest that this record was achieved despite the presence of retinopathy and nephropathy in one half of the patients However, White's suggestion (5a) that therapy with estrogens favorably affects the course and outcome of such pregnancies, though followed by some clinics (2p, 6b–e), has not been universally accepted Other workers have been unable to relate high levels of gonadotropins and low levels of estrogens and pregnandiol to fetal mortality (6f g) It has been indicated moreover, that close supervision (2e, 5m n 6h–j) and delivery at 36–38 weeks (2d, 6h, i) themselves yield comparable improvement in statistics

B The Prediabetic Syndrome

It is to be noted, however, that the existence of the prediabetic syndrome characterized by increased fetal loss and birth of large babies makes it probable that the achievement of a perfect control of diabetes can by itself never reduce fetal mortality to that present in the nondiabetic population as a whole Miller *et al* (7a–c) Kriss and Futcher (7d), and others (7e f) have shown that nondiabetic women who give birth to large infants are more apt to develop diabetes at a later date In the Kriss and Futcher series (7d) the probability was 60 per cent in those delivered of infants weighing thirteen pounds or more Jackson (7g–i) has shown that the syndrome may be manifest in the male parent as well, though there of course the birth of a large baby should not prove to be a precursor of maternal diabetes

Study of the rates of abortions, premature deaths, stillbirths, and toxemias in this prediabetic state as it occurs in females reveals an increased frequency several decades before the appearance of clinical diabetes (7a–

c, e, 8a, b) (table 25 II) Miller (7c) has pointed out that the statistics in the so called nonconfirmatory studies of Dolger and Herzstein (8c, d) actually support the concept, though the frequency of such manifestations of the prediabetic syndrome is still disputed (8e)

The existence of the prediabetic syndrome points to a somatic or germinal defect in the parents or in the product of conception which becomes manifest when carbohydrate metabolism is in all probability normal Hence, the maximal result to be expected at this time from ideal and successful regimens of diabetic control is the elimination of the deaths which hypoglycemia and ketoacidosis superimpose upon this inherited predisposition to a high rate of fetal loss This means, of course, that emphasis at least equal to that given to diabetic control should be given to a search for other variables in the hope they can be modified or circumvented The prevention of hydramnios and of toxemia are examples of the former while the beneficial effects of delivery at 36–38 weeks, first advocated by Lambie (8f) three decades ago, and perhaps the controversial issue of hormonal therapy discussed above, illustrate the latter (8g–i)

C Morphologic Changes in Infants of Diabetic Mothers Gross and Microscopic

Earlier it has been pointed out that 11 to 72 per cent of the fetuses which reached term or survival age, 28 weeks or more, in various series were then lost by stillbirth or neonatal deaths The higher incidence of large babies in diabetic and potentially diabetic mothers has also been mentioned To these gross morphologic facts a third can be added the incidence of congenital anomalies among such offspring is up to six times greater than that in the nondiabetic population (1h, 2g, 5a, 9a, b), though this may not be evident in smaller series (2a, m, 4b, 5k)

To date a number of changes have been documented as present in some but not all autopsies of stillbirth and neonatal deaths of infants born to diabetic mothers Thus, measurements of the volume of pancreatic islets

also occurs in infants of nondiabetic mothers (10h, i) and may be ... to adrenocortical hyperactivity (10i–n) The incidence of pulmonary hyaline membrane appears to be higher in infants in whom there is no obvious cause of death than in those who have lesions believed sufficient to have proved fatal (11a b) This may be merely a reflection of prematurity (11d h) and the more frequent recourse to Caesarean section and delivery at the thirty sixth to thirty eighth week in modern care of pregnant dia

betic patients Also, erythropoiesis in the liver and spleen has been observed in about one-half of the autopsied infants (10f, 11c) Finally, in keeping with the radiographic evidence of transient cardiomegaly in infants who survive (10g), cardiac enlargement has been demonstrated at autopsy (11c)

D Biochemical Changes in the Neonatal Period

1. Blood Sugar Concentrations. For many years there has been much concern over the tendency of these infants to develop hypoglycemia following birth This was logical to the extent that the pancreatic islets were known to be increased in size (10b–g) Various regimens of glucose administration were used to counteract the low blood sugar levels found in infants born of diabetic mothers (12a–f) However, control observations on infants of nondiabetic mothers to determine whether this was an undue or a characteristic degree of neonatal hypoglycemia were lacking When these became available (12b–h) (see figure 25-1) it was realized that pronounced asymptomatic lowering of blood sugar levels after birth was a

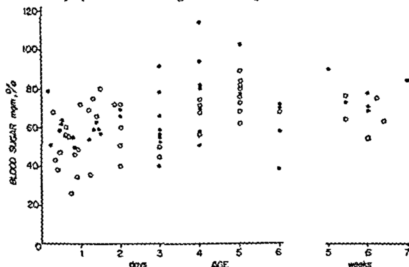


Fig 25-1 Venous Blood Sugar Values in Healthy Infants Born of Nondiabetic Mothers

Low blood sugar levels were present in about one-half of this group of healthy male (solid circle) and female (open circle) infants born at the Elizabeth Steel Magee Hospital Measurements during the first 12 hours were made in fasting newborns Subsequent samples were obtained 3 or 4 hours following the last feeding Our findings are in keeping with the observations of others and indicate that low blood sugar concentrations are not limited as hitherto believed to infants born of diabetic mothers (12g)

physiologic event in many *infants of both diabetic and nondiabetic* mothers and usually did not require special therapy (2f, 12b–f). However, this is by no means a universal view (12i).

2. Serum Anion-Cation (Acid Base) Balance. Measurements of the total CO_2 content and pH of the sera in infants of diabetic mothers during the neonatal period have revealed the *lowering of serum bicarbonate levels* characteristically present in the pregnant adult female and the normal newborn infant (5l). The work of Marples and Lippard (13b, c), of Branning (*13d*), and of others (*13e, f*) in normal infants beyond the neonatal period has indicated this to be a compensated metabolic acidosis (pH values are normal) secondary to hyperchloremia and at times to a lowering of sodium concentrations for undetermined reasons. This is to be differentiated from the uncompensated respiratory acidosis with increased P_{CO_2} *and decreased pH values known to be present in the first few hours following birth* (13f). In the infants of diabetic mothers there has been noted a prolongation of this unexplained early respiratory acidosis (5l). The changes in the other electrolytes have shown no pattern (5l, 13a).

Recently Engleson and Bjorklund (14) have suggested that potassium *deficiency may be the cause of sudden cyanosis and cardiac dilatation* in infants who appeared perfectly well at delivery. Kass (14) has observed one infant who collapsed suddenly 13 hours after birth with electrocardiographic evidence compatible with hypokalemia present. Within three hours of the administration of ½ gram of potassium chloride by stomach tube the *electrocardiographic changes* disappeared. The infant recovered uneventfully after further dosage with potassium chloride in the third, fourth, and fifth days of life. Zetterstrom and Aberg have noted marked potassium retention and sodium diuresis in newborn infants of diabetic mothers, suggesting that intracellular sodium stores were increased at birth (15a). The presence of corticoids in the amniotic fluid of a pregnant diabetic suggests that adrenocortical hyperactivity plays a role in these cell potassium and sodium changes (15b), as does the high urinary excretion of oxysteroids and of *17-ketosteroids by infants born of diabetic mothers* (15c).

Summary

t

is generally recognized that pregnancy in the diabetic ... ance for carbohydrate and that the insulin need rises. Though ketosis and acidosis from this or other causes may precipitate such fetal accidents, ... regulation of diabetes is not the usual cause. The existence of

ing

this

possibility Neither does the explanation lie in the lower fetal and neo natal mortality reported in some clinics employing estrogen therapy since this record can be matched by improvement of antenatal care and earlier delivery An undue incidence of congenital anomalies, hyaline membrane formation cardiomegaly, and extramedullary hematopoiesis is found at autopsy of such infants

The hypoglycemia of the infant born to a diabetic mother is usually no greater than that seen in the nondiabetic population There is evidence however that anion cation patterns of such infants may be abnormal

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CHAPTER 26

The Occurrence of Neuropathy, Insulinogenic Lipodystrophy and Necrobiosis Lipoidica in Diabetics

The child or adult may develop three other concomitants sequelae or complications of *diabetes mellitus in addition to the ketoacidosis altered* growth and development vascular disease duodenal ulcer and hepatic *dysfunction discussed in preceding chapters* Neuropathy the first of these *fortunately spares the juvenile diabetic at least during the early years of* the childhood phase of the disorder but can be severe and disabling in the older patients Another insulinogenic lipodystrophy is relatively unimportant and occurs more often in children than in adults The third necrobiosis lipoidica is infrequent as an extensive manifestation

I Neuropathy

In the patient who develops diabetes mellitus after reaching maturity *neuropathy is a distressing and if all symptoms and signs are taken into* account a relatively frequent complication (1a m 2a f h 3a g 4a b *5a–d) The actual incidence is in doubt however because not all workers* accept as Jordan (1a) Rundles (1b c) Goodman *et al* (1d) and others (1e f) have *that* any pain or paresthesia occurring in the diabetic is to be ascribed to diabetes In these series neurologic changes were present in 50 to 93 per cent or more of the patients

The manifestations can take the form of a) peripheral neuritis which is especially apt to involve the sensory component producing paresthesia (dysesthesia too *i e* a perverted interpretation of sensation) pain which is often worse at night hypo or areflexia and impairment of perception *of vibration joint position and* less *commonly* of pin prick and touch sensation (cranial nerves also are affected with extraocular muscle palsy *(2a h) and with pupillary changes but these may reflect* involvement of the pretectal area of the brain) b) possible dorsal column disease with impairment of vibratory and *position senses (though these changes may* result from peripheral neuritis alone) and with evidences of tabes diabetica (2f 3a g) c) central nervous system dysfunction with *encephalopathy*

(1a–e, g), d) autonomic system disease evidenced by vasomotor instability, hypotension, dizziness, decreased sweating, bladder atony, impotence, diarrhea or constipation (1a f, 4a–c, 5a–d), and e) combined involvement as of the autonomic system and the peripheral nerves in Charcot joints and trophic ulcers

It should be pointed out, however, that the precise nature of such neurologic disturbances and the mechanisms whereby their manifestations are produced have not been firmly established Thus in the case of orthostatic hypotension first reported two decades ago (5c) and described at intervals since then (5f g) the decrease in blood pressure with changes in posture has been attributed to nervous mechanisms It has been proposed that defective arterial vasoconstriction (5f g) an inadequate reflex autonomic response to pooling of blood in the dependent parts of the body (5h) and segregation of blood in the capillary and venous system (5i) were responsible (5j)

A Etiology and Clinical Course of Diabetic Neuropathy

In some of the studied cases evidences of arteriosclerotic changes in the vasa nervorum have been found (6a) This has been taken to represent a further instance of the diabetic s susceptibility to vascular diseases However, there is no necessary correlation between occlusive vascular changes in the diabetic and the occurrence of neuropathy (6b) In those patients in whom the vessels are intact the neuropathy is attributed to biochemical disturbances occurring in the course of diabetes (1d), or to some unidentified dysfunction of vitamin metabolism (3g 7) Recently Fagerberg has suggested that diabetic neuropathy has the same pathogenesis as retinopathy and nephropathy (6c)

The work of Mirsky *et al* (3b c) and of others (3g) supports the view that irrespective of its etiology the neuropathy is evidence of another *locus minoris resistentiae* in the diabetic since it can appear before there is evidence of the diabetes itself The high incidence of neuropathy in diabetics as a group does not, of course exclude degenerative central nervous sytem diseases tumors and even porphyria (8a) as possible etiologic factors of neurologic disorders in some diabetic patients

The clinical onset of diabetic neuropathy may assume one of several forms Most often the peripheral neuritis or other neurologic abnormality occurs in the course of unregulated diabetes which has been present for several years but may be of relatively recent onset, with regulation improvement can but need not appear (1d c) In other cases the neuropathy becomes manifest as diabetic control is imposed upon previously inadequately treated cases The latter is relatively infrequent, making up less than two per cent of the series reported by Goodman *et al* (1d)

B Incidence of Neuropathy in Juvenile Diabetics

Pain on the basis of peripheral neuritis, so common in adult diabetics, has not been described and is but rarely encountered, if at all, in the early years of juvenile diabetes Moreover in at least one study it has been reported that vibratory sense, which is a functional elaboration of touch, position, and pressure (8b–e), is intact in juvenile diabetics under the age of ten (3d) However, in this group of patients there were many in the 10 to 20-year-old group (18 out of 44) who did have evidence of vibratory

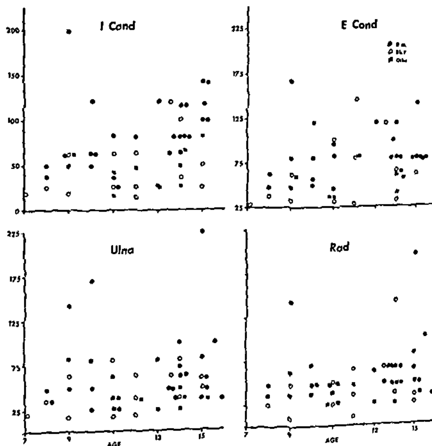


Fig 26 1 Vibratory Perception in Juvenile Diabetics

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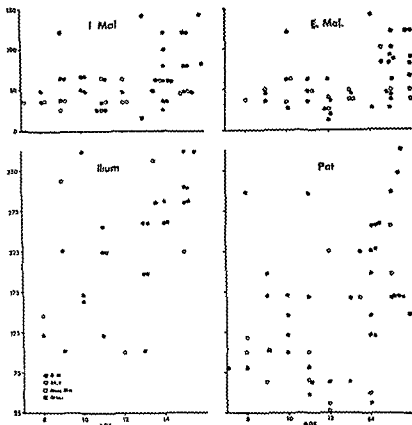


FIG 26-2 VIBRATORY PERCEPTION IN JUVENILE DIABETICS
Legend as in fig 26-1

impairment The involvement ranged up to a 40 per cent loss in the upper extremities and as much as a 70 per cent decrease in the lower Our findings, based on quantitative measurements of the vibratory sense in children are shown in figures 26-1 and 26-2 (8f) The rise in threshold which occurs with age is quite definite in test areas in which the range of variation from patient to patient is small Two of our patients in the nine- and ten year age group were the youngest in whom impaired perception was present

A number of other authors (1a b) have included occasional juvenile diabetics who developed neuropathy before or after reaching adulthood These are listed in table 26 I Perhaps the most troublesome of these are the patients with diarrhea which is watery and tends to be nocturnal The

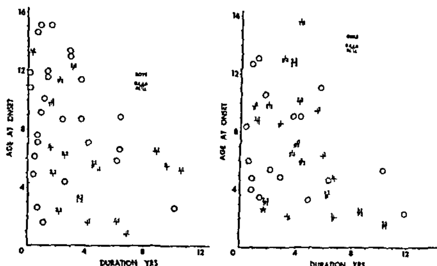


FIG 26-3 INSULINOGENIC ATROPHY IN DIABETIC CHILDREN

Circles refer to patients without atrophy numerals in quadrants indicate diameter of atrophic areas in inches on right and left arms (RA LA) and right and left legs (RL LL) In this cross-sectional survey of a group of our diabetic patients atrophy occurred somewhat more often and was more marked in girls than in boys With but one exception atrophy did not appear in this series during the first year of diabetes

these possibilities were subsequently excluded by suitable clinical and experimental trials (10o, 11e) The belief that the type of insulin affected the incidence (11f) has not been substantiated (11g)

The findings in our series (figure 26 3) are in keeping with the reports of Marble *et al* (11b) who found atrophy in 40 per cent of the male and 50 per cent of the female juvenile diabetics after 12 months of therapy or longer In adults the incidents is lower ranging down to seven per cent (11b, g) and occurring largely but not exclusively in females Atrophy has also been reported in a nondiabetic female (11h) who received insulin for three weeks in an attempt to stimulate body weight gain This preponderance in females may be related to the thicker layer of subcutaneous fat (11i j), though Marble's studies have shown no correlation with obesity as such In a group of our diabetic children the subcutaneous fat in 66 boys averaged 0 45 cm and 0 55 cm in 45 girls

It has been suggested on the basis of patients whose insulin requirement rose during hypertrophy and in others who developed atrophy that these local reactions are causes of ' brittle ' diabetes (see Chapter 16) presumably by interfering with insulin absorption (11k) This has not been our experience

B "Hypertrophy" at Sites of Insulin Injection

As the choice of the term lipodystrophy implies, swelling or "hypertrophy" at the sites of insulin injection has also been noted (11a, b, k) However, there have been no detailed statements of the relative incidence of swelling and of atrophy Neither is it clear that swelling inevitably results in atrophy Our own observations on these points are limited to a cross sectional rather than a sequential survey (figure 26-4 and table 26 II) Swelling alone was present in 39 per cent of the boys and 44 per cent of

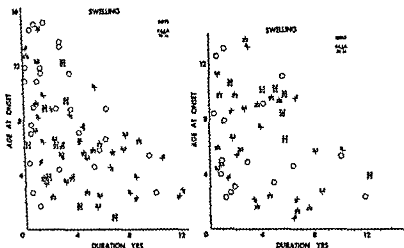


Fig 26-4 Swelling or "Hypertrophy" at Sites of Insulin Injection

In this group of diabetic children under our care swelling occurred with approximately equal frequency and to an equal degree in boys and girls (Zero indicates none and numerals in 4 quadrants indicate diameter of involved area in inches)

TABLE 26 II

Incidence of swelling and atrophy at insulin injection sites

Duration of Diabetes	yrs																									
	0-1		1 2		2-3		3-4		4-5		5-6		6-7		7-8		8-9		9-10		10 11		11 12		12-13	
	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−	+	−
BOYS																										
Swelling	9	5	5	10	4	6	2	5	1	6	2	5	2	3	0	2	0	4	1	0	1	1	0	1	0	1
Atrophy	10	1	5	3	4	3	2	2	1	3			3	2			0	1	0	1	1	1				
GIRLS																										
Swelling	4	5	3	5	1	5	0	4	2	3	1	5	1	4	0	1	0	2			1	1	1	0	0	1
Atrophy	5	1	3	5	2	2	1	4	1	4	1	2	1	3			0	1			1	1	1	0		

the girls, the incidence of atrophy without associated swelling was seven per cent and 16 per cent in the two groups respectively Both atrophy and swelling were encountered in 11 per cent of the boys and 16 per cent of the girls Freedom from both atrophy and swelling was observed almost twice as often in the male as in the female juvenile diabetics

C Therapy of Subcutaneous Hypertrophy and Atrophy Induced by Insulin Injections

Repeatedly various workers beginning with Depisch and Barborka in 1926 have suggested that the sites of injection be rotated to minimize these local reactions (10a, b, s, z, 11b) This view unfortunately has only served to increase the number of involved areas Boller thought that cocaine or novacaine might be effective as a preventive (10r), a hope which has not been realized

More recently there have been several suggestions which appear worthy of trial Collens *et al* (111) have shown that reinjection of atrophic sites with the daily dosage of insulin decreases the magnitude of the deformity without discernible influence on diabetic control Workers in England (Fox, McConnell, Pemberton, and Watson (11m)) have reported that the admixture of hyaluronidase and insulin prevented the development of new areas of atrophy in previously susceptible children despite one and one half years of therapy without rotation of sites They used 3 mg of hyaluronidase per 400 units of insulin in a mixture prepared within eight hours of use Duncan *et al* (11n) believe that allowing refrigerated insulin to reach room temperatures before use eliminates or minimizes these local changes

Finally, spontaneous disappearance of atrophic areas may occur Chapman (10f) has described a patient in whom subcutaneous tissue lost after large injections of insulin in the left thigh reappeared without therapy two and one-half years later

III. Necrobiosis Lipoidica Diabeticorum and *Xanthoma Eruptivum* (Diabeticum)

Necrobiosis lipoidica diabeticorum when present usually affects the lower extremities of women (12a–j) We have seen two examples of this skin change in former juvenile diabetics (figure 26 5) It may also occur in nondiabetics (12k) It begins as red papules which enlarge at the periphery and become depressed in the center leaving a plaque-like ring with a yellow-purplish tinge The skin becomes tense and atrophic and telangiectases appear (12a) Histologic examination of 41 cases by Laymon and Fisher (12b) revealed necrobiotic changes in the collagen with increased lipids and diffuse cellular infiltration Some workers suggest that this lesion must be differentiated from granuloma annulare (12b, c) They point



Fig. 26-5A. Necrobiosis Lipoidica Diabeticorum

This 2[illegible]-year-old female (W. S.) developed diabetes at the age of 9 years and first noted lesions on extremities at age of 9½ years. Lesion shown above is on left thigh. Subsequently the patient developed glaucoma which was treated by enucleation at the ages of 21 and 21½ years at another institution.



Fig. 26-5B. Necrobiosis Lipoidica Diabeticorum

Photomicrograph of necrobiosis lipoidica diabeticorum with area of necrosis of *collagen at lower center in biopsy obtained from lesion on left thigh shown in figure* 26-5A. (The authors are indebted to Dr. Mark Bracken for the above photomicrograph.)

out that in necrobiosis lipoidica diabeticorum there is less tendency to palisading of cellular infiltrate around the necrobiotic collagen and that fibrosis of the walls of the blood vessels with proliferation of the intimal lining are more apt to be present; mucin is absent in contrast to its presence in granuloma annulare (12c). It may well be, however, that these two lesions are merely variants of one another.

It has been recognized that xanthomatous skin lesions, including palpebral xanthelasma, may appear in unregulated diabetics and decrease or disappear with adequate control (13a–f). This manifestation is related to the associated hyperlipemia with an increase in the S_f 20–100 and 100–400 lipoproteins (13g) rather than to the diabetes *per se*. It has been suggested (13b) that the most appropriate term for this skin change is xanthoma eruptivum (diabeticum).

Summary

Neuropathy is an infrequent occurrence in juvenile diabetics during their early course, but diabetics of all ages may develop peripheral neuropathy, impairment of vibratory sense, cerebral and cranial nerve disturbances, or autonomic disorders. Though these generally occur in inadequately controlled diabetics, they may first appear in patients as satisfactory control is achieved. Therapy is empiric and must be persistent.

Insulinogenic lipodystrophy, i.e., swelling or atrophy at the sites of insulin injection, develops more often in females than in males and in children than in adults. The origins of these changes are obscure and views on therapy are varied.

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